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(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GABOS, Balint** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **LUNDKVIST, Michael** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **MUNCK AF ROSENSCHÖLD, Magnus** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **SHAMOVSKY, Igor** [CA/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE).

(74) Agent: **ASTRAZENECA AB**; Global Intellectual Property, S-151 85 Södertälje (SE).

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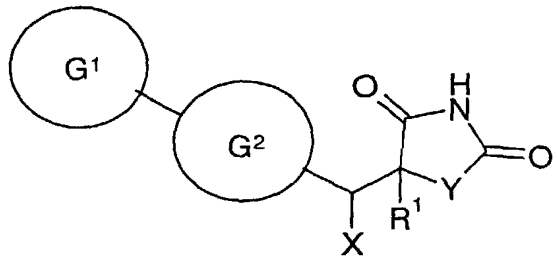

(I)

(57) Abstract: The invention provides compounds of formula, in which X, Y, R^1, G^1 and G^2 have the meanings defined in the specification; processes for their preparation; pharmaceutical compositions containing them; a process for preparing the pharmaceutical compositions; and their use in therapy.

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COMPOUNDS

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

Metalloproteinases are a superfamily of proteinases (enzymes) whose numbers in recent years have increased dramatically. Based on structural and functional considerations these enzymes have been classified into families and subfamilies as described in N.M. Hooper (1994) FEBS Letters 354:1-6. Examples of metalloproteinases include the matrix metalloproteinases (MMPs) such as the collagenases (MMP1, MMP8, MMP13), the gelatinases (MMP2, MMP9), the stromelysins (MMP3, MMP10, MMP11), matrilysin (MMP7), metalloelastase (MMP12), enamelysin (MMP19), the MT-MMPs (MMP14, MMP15, MMP16, MMP17); the reprolysin or adamalysin or MDC family which includes the secretases and sheddases such as TNF converting enzymes (ADAM10 and TACE); the astacin family which include enzymes such as procollagen processing proteinase (PCP); and other metalloproteinases such as aggrecanase, the endothelin converting enzyme family and the angiotensin converting enzyme family.

Metalloproteinases are believed to be important in a plethora of physiological disease processes that involve tissue remodelling such as embryonic development, bone formation and uterine remodelling during menstruation. This is based on the ability of the metalloproteinases to cleave a broad range of matrix substrates such as collagen, proteoglycan and fibronectin. Metalloproteinases are also believed to be important in the processing, or secretion, of biological important cell mediators, such as tumour necrosis factor (TNF); and the post translational proteolysis processing, or shedding, of biologically important membrane proteins, such as the low affinity IgE receptor CD23 (for a more complete list see N. M. Hooper *et al.*, (1997) Biochem J. 321:265-279).

Metalloproteinases have been associated with many diseases or conditions. Inhibition of the activity of one or more metalloproteinases may well be of benefit in these diseases or conditions, for example: various inflammatory and allergic diseases such as, inflammation of the joint (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastro-intestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), inflammation of the skin (especially psoriasis, eczema, dermatitis); in tumour metastasis or invasion; in disease associated with uncontrolled degradation of the extracellular matrix such as osteoarthritis; in bone resorptive disease (such as osteoporosis and Paget's disease); in diseases associated with aberrant angiogenesis; the enhanced collagen remodelling associated with diabetes, periodontal disease (such as gingivitis), corneal ulceration, ulceration of the skin, post-operative conditions (such as colonic anastomosis) and dermal wound healing; demyelinating diseases of the central and peripheral nervous systems (such as multiple sclerosis); Alzheimer's disease; extracellular matrix remodelling observed in cardiovascular diseases such as restenosis and atheroscelerosis; asthma; rhinitis; and chronic obstructive pulmonary diseases (COPD).

MMP12, also known as macrophage elastase or metalloelastase, was initially cloned in the mouse by Shapiro *et al* [1992, Journal of Biological Chemistry 267: 4664] and in man by the same group in 1995. MMP12 is preferentially expressed in activated macrophages, and has been shown to be secreted from alveolar macrophages from smokers [Shapiro *et al*, 1993, Journal of Biological Chemistry, 268: 23824] as well as in foam cells in atherosclerotic lesions [Matsumoto *et al*, 1998, Am J Pathol 153: 109]. A mouse model of COPD is based on challenge of mice with cigarette smoke for six months, two cigarettes a day six days a week. Wildtype mice developed pulmonary emphysema after this treatment. When MMP12 knock-out mice were tested in this model they developed no significant emphysema, strongly indicating that MMP12 is a key enzyme in the COPD pathogenesis. The role of MMPs such as MMP12 in COPD (emphysema and bronchitis) is discussed in Anderson and Shinagawa, 1999, Current Opinion in Anti-inflammatory and Immunomodulatory Investigational Drugs 1(1): 29-38. It was recently discovered that

smoking increases macrophage infiltration and macrophage-derived MMP-12 expression in human carotid artery plaques Kangavari [Matetzky S, Fishbein MC *et al.*, Circulation 102:(18), 36-39 Suppl. S, Oct 31, 2000].

MMP9 (Gelatinase B; 92kDa TypeIV Collagenase; 92kDa Gelatinase) is a secreted protein which was first purified, then cloned and sequenced, in 1989 [S.M. Wilhelm *et al* (1989) J. Biol Chem. 264 (29): 17213-17221; published erratum in J. Biol Chem. (1990) 265 (36): 22570]. A recent review of MMP9 provides an excellent source for detailed information and references on this protease: T.H. Vu & Z. Werb (1998) (In : Matrix Metalloproteinases. 1998. Edited by W.C. Parks & R.P. Mecham. pp115 - 148. Academic Press. ISBN 0-12-545090-7). The following points are drawn from that review by T.H. Vu & Z. Werb (1998).

The expression of MMP9 is restricted normally to a few cell types, including trophoblasts, osteoclasts, neutrophils and macrophages. However, it's expression can be induced in these same cells and in other cell types by several mediators, including exposure of the cells to growth factors or cytokines. These are the same mediators often implicated in initiating an inflammatory response. As with other secreted MMPs, MMP9 is released as an inactive Pro-enzyme which is subsequently cleaved to form the enzymatically active enzyme. The proteases required for this activation *in vivo* are not known. The balance of active MMP9 versus inactive enzyme is further regulated *in vivo* by interaction with TIMP-1 (Tissue Inhibitor of Metalloproteinases -1), a naturally-occurring protein. TIMP-1 binds to the C-terminal region of MMP9, leading to inhibition of the catalytic domain of MMP9. The balance of induced expression of ProMMP9, cleavage of Pro- to active MMP9 and the presence of TIMP-1 combine to determine the amount of catalytically active MMP9 which is present at a local site. Proteolytically active MMP9 attacks substrates which include gelatin, elastin, and native Type IV and Type V collagens; it has no activity against native Type I collagen, proteoglycans or laminins.

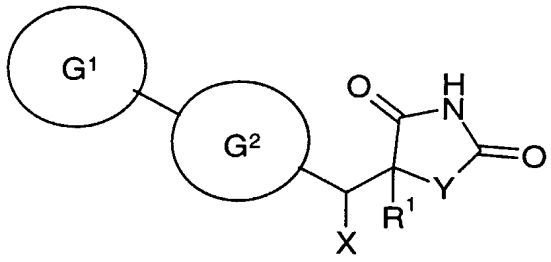
There has been a growing body of data implicating roles for MMP9 in various physiological and pathological processes. Physiological roles include the invasion of embryonic trophoblasts through the uterine epithelium in the early stages of embryonic implantation; some role in the growth and development of bones; and migration of inflammatory cells from the vasculature into tissues.

MMP9 release, measured using enzyme immunoassay, was significantly enhanced in fluids and in AM supernantants from untreated asthmatics compared with those from other populations [Am. J. Resp. Cell & Mol. Biol., Nov 1997, 17 (5):583-591]. Also, increased MMP9 expression has been observed in certain other pathological conditions, thereby implicating MMP9 in disease processes such as COPD, arthritis, tumour metastasis, Alzheimer's, Multiple Sclerosis, and plaque rupture in atherosclerosis leading to acute coronary conditions such as Myocardial Infarction.

A number of metalloproteinase inhibitors are known (see for example the reviews of MMP inhibitors by Beckett R.P. and Whittaker M., 1998, Exp. Opin. Ther. Patents, 8(3):259-282, and by Whittaker M. *et al*, 1999, Chemical Reviews 99(9):2735-2776).

We have now discovered a new class of compounds that are inhibitors of metalloproteinases and are of particular interest in inhibiting MMPs such as MMP12 and MMP9. In particular, we have discovered compounds that are potent dual MMP12 and MMP9 inhibitors and have desirable activity profiles. The compounds of this invention have beneficial potency, selectivity and/or pharmacokinetic properties.

In accordance with the present invention, there is therefore provided a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof



(I)

wherein

X represents –OH, $-NH_2$, $-NH(C_1-C_3$ alkyl) or –SH;

Y represents $-NR^2$ where R^2 represents hydrogen or C_1-C_4 alkyl;

R^1 represents hydrogen, or a group selected from C_1-C_6 alkyl and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, carboxyl, $-NR^3R^4$, $-CONR^5R^6$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonyl(oxy), $-S(O)_mC_1-C_6$ alkyl where m is 0, 1 or 2, C_1-C_6 alkylsulphonylamino, C_1-C_6 alkoxycarbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo (=O), carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl and C_1-C_6 hydroxyalkyl;

R^3, R^4, R^5 and R^6 each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

G^2 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring;

G^1 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring which may be optionally fused to a second ring to form a bicyclic ring system containing a total of 8- to 10-ring atoms, the monocyclic ring or fused bicyclic ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo (=O), cyano, nitro, C_1-C_6 alkyl (optionally substituted by one or more of cyano, halogen, hydroxyl and methoxy), C_2-C_6 alkenyl, C_1-C_6 alkoxy (optionally substituted by one or more halogen atoms), $-S(O)_nC_1-C_6$ alkyl where n is 0, 1 or 2 (optionally substituted by

one or more halogen atoms), C_1-C_6 alkylcarbonyl(amino) (optionally substituted by one or more halogen atoms), C_1-C_6 alkylcarbonyloxy, phenyl, benzyloxy, $-NR^7R^8$ and a group –V-U-W;

R^7 and R^8 each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

V represents $-CH_2$, $-OCH_2$, $-CH_2O$, -O, -S, -SO, $-SO_2$, $-O-SO_2$, $-SO_2-O$, -NH, -NHC(O), -C(O)NH, -O-C(O)NH, -NHC(O)NH, $-NHSO_2$, $-SO_2NH$ or -C(O);

U represents C_1-C_5 alkylene; and

W represents a direct bond to G^1 or a group selected from hydrogen, hydroxyl, amino ($-NH_2$), cyano, (di)C_1-C_3 alkylamino, C_1-C_3 alkylamido, C_1-C_3 alkylcarbamate, C_1-C_3 alkylurea, C_1-C_3 alkylsulphonyl, imidazolyl, oxazolyl and thiazolyl.

In the context of the present specification, unless otherwise stated, an alkyl or alkenyl substituent group or an alkyl moiety in a substituent group may be linear or branched. Similarly, an alkylene moiety may be linear or branched. A hydroxyalkyl substituent may contain one or more hydroxyl groups but preferably contains one or two hydroxyl groups. The alkyl moieties in a dialkylamino group may be the same or different. In the definition of R^1, it should be understood that each of the saturated or unsaturated 3- to 10-membered ring system and the saturated or unsaturated 5- to 6-membered ring may have alicyclic or aromatic properties. An unsaturated ring system will be partially or fully unsaturated. Further, in G^1, the second ring in the bicyclic ring system need not be aromatic and may contain one or more ring heteroatoms selected from nitrogen, oxygen and sulphur.

In an embodiment of the invention, X represents –OH.

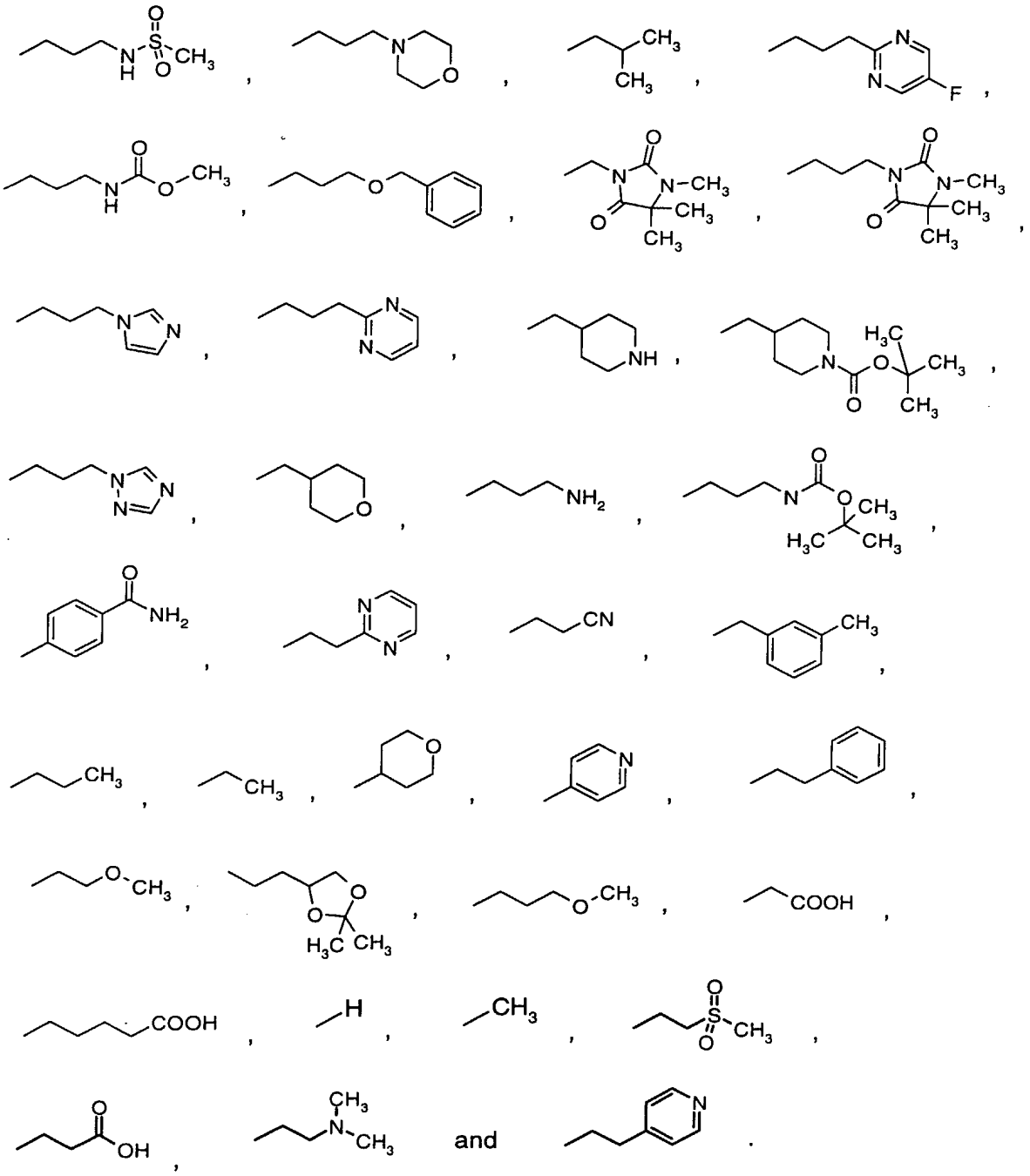
In an embodiment of the invention, Y represents $-NR^2$ where R^2 represents hydrogen or C_1-C_4 alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl or t-butyl. In another embodiment, Y represents NH.

In an embodiment of the invention, R^1 represents hydrogen, or a group selected from C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur,
each group being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, cyano, carboxyl, $-NR^3R^4$, $-CONR^5R^6$, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_1-C_6, preferably C_1-C_4, alkylcarbonyl(oxy) (e.g. methylcarbonyl(oxy), ethylcarbonyl(oxy), n-propylcarbonyl(oxy), isopropylcarbonyl(oxy), n-butylcarbonyl(oxy), n-pentylcarbonyl(oxy) or n-hexylcarbonyl(oxy)), $-S(O)_mC_1$-C_6, preferably C_1-C_4, alkyl where m is 0, 1 or 2 (e.g. methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl), C_1-C_6, preferably C_1-C_4, alkylsulphonylamino (e.g. methylsulphonylamino, ethylsulphonylamino, n-propylsulphonylamino, isopropylsulphonylamino, n-butylsulphonylamino, n-pentylsulphonylamino or n-hexylsulphonylamino), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl(amino) (e.g. methoxycarbonyl(amino), ethoxycarbonyl(amino), n-propoxycarbonyl(amino) or n-butoxycarbonyl(amino)), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, oxo, carboxyl, cyano, C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), C_1-C_6, preferably C_1-C_4, alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl) and C_1-C_6, preferably C_1-C_4, hydroxyalkyl (e.g. $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH(OH)CH_3$).

Examples of saturated or unsaturated 3- to 10-membered ring systems that may be used, which may be monocyclic or polycyclic (e.g. bicyclic) in which the two or more rings are fused, include one or more (in any combination) of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]heptyl, cyclopentenyl, cyclohexenyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, diazabicyclo[2.2.1]hept-2-yl, naphthyl, benzofuranyl, benzothienyl, benzodioxolyl, quinolinyl, 2,3-dihydrobenzofuranyl, tetrahydropyranyl, pyrazolyl, pyrazinyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, pyridazinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, indolyl, imidazolyl, pyrimidinyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl. Preferred ring systems include phenyl, pyridinyl and tetrahydropyranyl.

Examples of saturated or unsaturated 5- to 6-membered ring substituents in R^1 include cyclopentyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiomorpholinyl, pyrazolyl, pyrazinyl, pyridazinyl, thiazolidinyl, thienyl, isoxazolyl, pyrimidinyl, thiadiazolyl, pyrrolyl, furanyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl and pyridinyl. Preferred rings include morpholinyl, pyrimidinyl, phenyl, imidazolyl, piperidinyl, tetrahydropyranyl and triazolyl.

Particular values for R^1 include the following:



In another embodiment of the invention, R^1 represents hydrogen, or a group selected from C_1-C_4 alkyl and a saturated or unsaturated 5- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur,

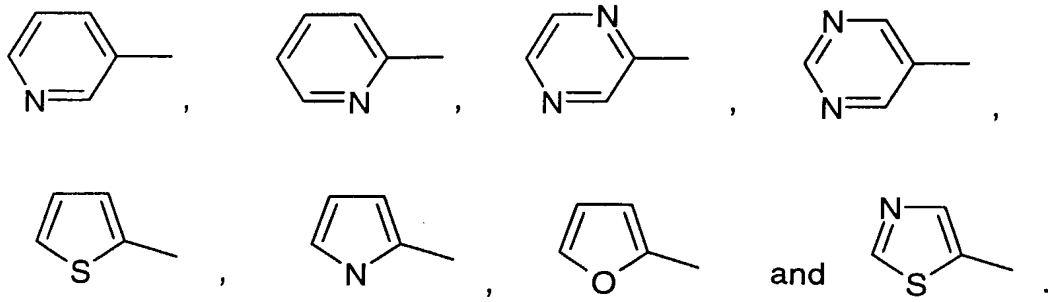
each group being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen, hydroxyl, cyano, carboxyl, $-NR^3R^4$, $-CONR^5R^6$, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylcarbonyl(oxy), $-S(O)_mC_1$-C_4 alkyl where m is 0, 1 or 2, C_1-C_4 alkylsulphonylamino, C_1-C_4 alkoxycarbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent (e.g. one, two or three substituents independently) selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxycarbonyl and C_1-C_4 hydroxyalkyl.

In still another embodiment, R^1 represents hydrogen or C_1-C_4 alkyl optionally substituted with a carboxyl substituent group.

R^3, R^4, R^5 and R^6 each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine) and C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

In an embodiment of the invention, R^3, R^4, R^5 and R^6 each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl, in particular methyl. In another embodiment, R^3, R^4, R^5 and R^6 each independently represent hydrogen.

G^2 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring. The heteroaryl ring will comprise one or more (e.g., one, two or three) ring heteroatoms independently selected from nitrogen, oxygen and sulphur. Examples of aryl and heteroaryl rings include phenyl, pyridinyl, thienyl, furanyl, pyrazinyl, pyrimidinyl, pyrrolyl and thiazolyl, for instance,



In an embodiment of the invention, G^2 represents phenyl.

G^1 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring which may be optionally fused to a second ring to form a bicyclic ring system containing a total of 8- to 10-ring atoms, the monocyclic ring or fused bicyclic ring system being optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, oxo, cyano, nitro, C_1-C_6, preferably C_1-C_4, alkyl such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen such as chlorine, fluorine, bromine or iodine, hydroxyl and methoxy, e.g. $-CF_3$), C_2-C_6, preferably C_2-C_4, alkenyl (e.g. ethenyl, prop-1-enyl, prop-2-enyl, but-1-enyl, pent-1-enyl, hex-1-enyl or 2-methyl-pent-2-enyl), C_1-C_6, preferably C_1-C_4, alkoxy such as methoxy, ethoxy, n-propoxy or n-butoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine, e.g. $-OCF_3$), $-S(O)_nC_1$-C_6, preferably C_1-C_4, alkyl where n is 0, 1 or 2 (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine) (e.g. methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl or $-SCF_3$),

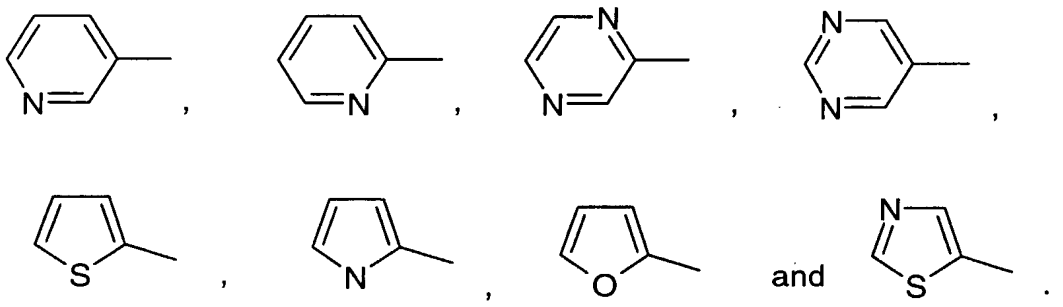
C_1-C_6, preferably C_1-C_4, alkylcarbonyl(amino) (optionally substituted by one or more, e.g. one, two or three, halogen atoms such as chlorine, fluorine, bromine or iodine) (e.g. methylcarbonyl(amino), ethylcarbonyl(amino), n-propylcarbonyl(amino), isopropylcarbonyl(amino), n-butylcarbonyl(amino), n-pentylcarbonyl(amino), n-hexylcarbonyl(amino) or -C(O)CF_3),

C_1-C_6, preferably C_1-C_4, alkylcarbonyloxy (e.g. methylcarbonyloxy, ethylcarbonyloxy, n-propylcarbonyloxy, isopropylcarbonyloxy, n-butylcarbonyloxy, n-pentylcarbonyloxy or n-hexylcarbonyloxy),

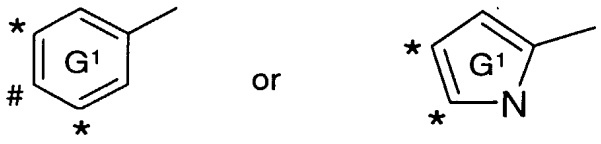
phenyl, benzyloxy, -NR^7R^8 and a group –V-U-W.

A 5- or 6-membered heteroaryl ring will comprise at least one ring heteroatom (e.g. one, two or three ring heteroatoms independently) selected from nitrogen, oxygen and sulphur.

Examples of 5- or 6- membered aryl or heteroaryl monocyclic rings include phenyl, pyridinyl, thienyl, furanyl, pyrazinyl, pyrimidinyl, pyrrolyl and thiazolyl, for instance,



If the 5- or 6- membered aryl or heteroaryl monocyclic ring is substituted, it is preferred that the substituent(s) are located in the *meta* and/or *para* positions, as illustrated in the examples below:



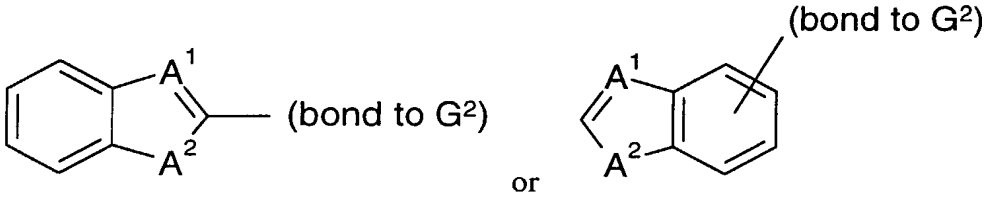
* denotes a *meta* substitution position; # denotes a *para* substitution position.

A preferred *meta* substituent is a C_1-C_3 alkyl group or $-CH_2CN$.

A preferred *para* substituent is Br, Cl, -CN, $-CF_3$, $-SCF_3$ or $-OCF_3$.

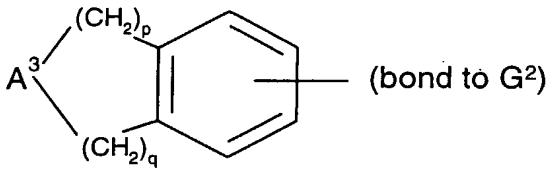
In an embodiment of the invention, in G^1, the 5- or 6- membered aryl or heteroaryl monocyclic ring is fused to a second ring to form a bicyclic ring system containing a total of 8- to 10-ring atoms.

For example, the bicyclic ring system may have the structure:



where A^1 is CH or N and A^2 is NH, O or S,

or may have the following structure:



where A^3 is NH, O or S, p is 1 and q is 1 or p is 1 and q is 2 or p is 0 and q is 3.

Specific examples of bicyclic ring systems include quinolinyl, isoquinolinyl, indolyl, tetrahydroisoquinolinyl, benzofuranyl, benzothienyl, quinazolinyl, phthalazinyl, dihydrobenzofuranyl, naphthyl and dihydroindolyl. Preferred bicyclic ring systems include quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, naphthyl, benzofuranyl and benzothienyl.

In one embodiment, G^1 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring which may be optionally fused to a second ring to form a bicyclic ring system containing a total of 8- to 10-ring atoms, the monocyclic ring or fused bicyclic ring system being optionally substituted with one, two or three substituents independently selected from halogen, hydroxyl, oxo, cyano, nitro, C_1-C_4 alkyl (optionally substituted by one or more, e.g. one, two or three, substituents independently selected from cyano, halogen, hydroxyl and methoxy), C_2-C_4 alkenyl, C_1-C_4 alkoxy (optionally substituted by one or more, e.g. one, two or three, halogen atoms), -$S(O)_n$$C_1$-$C_4$ alkyl where n is 0, 1 or 2 (optionally substituted by one or more, e.g. one, two or three, halogen atoms), C_1-C_4 alkylcarbonyl(amino) (optionally substituted by one or more, e.g. one, two or three, halogen atoms), C_1-C_4 alkylcarbonyloxy, phenyl, benzyloxy, -NR^7R^8 and a group -V-U-W.

R^7 and R^8 each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine) and C_1-C_6, preferably C_1-C_4, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

In an embodiment of the invention, R^7 and R^8 each independently represent hydrogen or C_1-C_6, preferably C_1-C_4, alkyl, in particular methyl. In another embodiment, R^7 and R^8 each independently represent hydrogen.

In an embodiment of the invention, V represents –O or -O-SO_2.

In an embodiment of the invention, U represents –CH_2- or –CH_2CH_2-.

In an embodiment of the invention, W represents hydrogen, (di)C_1-C_3 alkylamino (e.g. methylamino or dimethylamino) or C_1-C_3 alkylsulphonyl (e.g. methylsulphonyl).

Particular combinations of G^1 and G^2 include the following:

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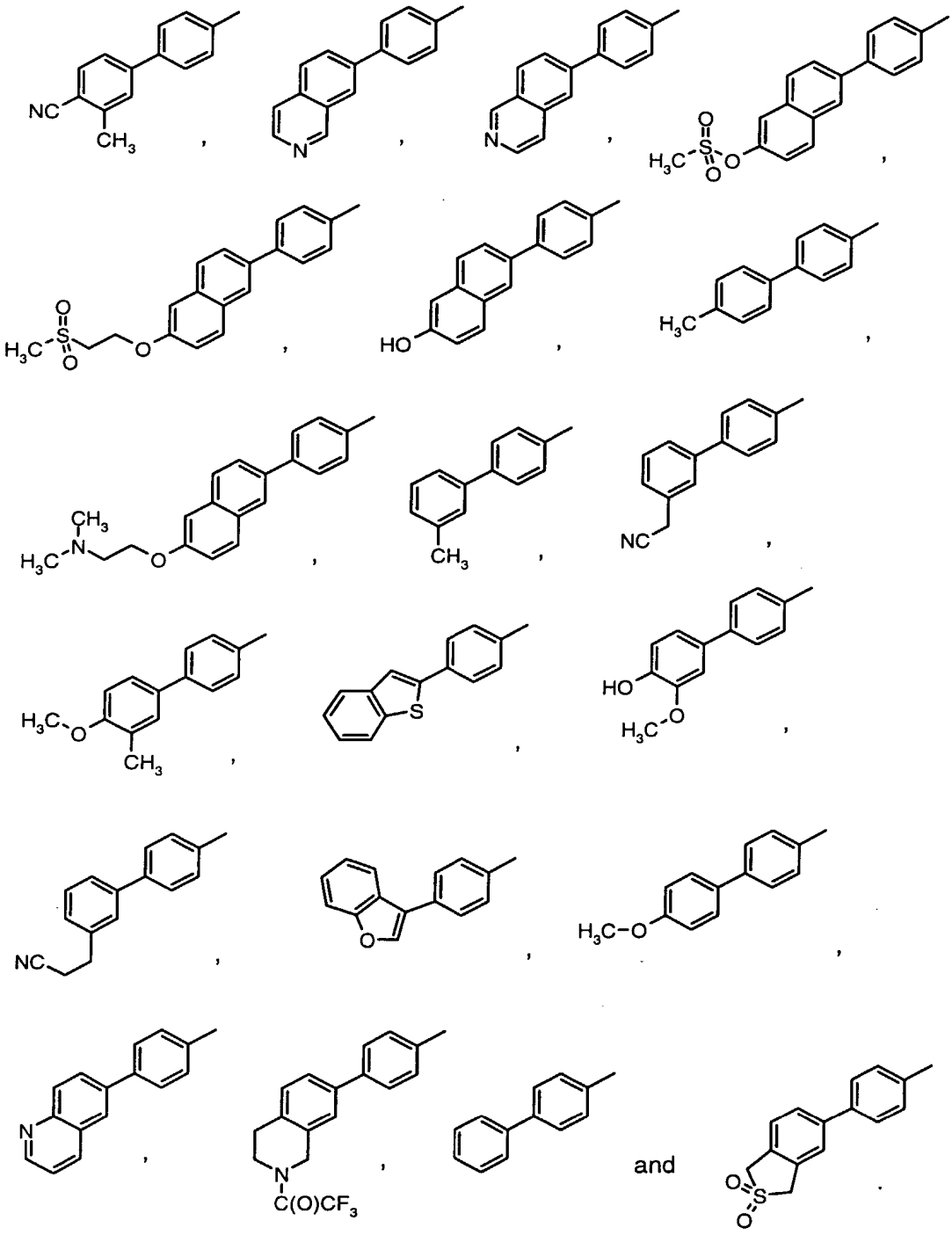


In an embodiment of the invention:

X represents –OH;

Y represents –NH;

R^1 represents hydrogen or C_1-C_4 alkyl optionally substituted with a carboxyl substituent group;

G^2 represents phenyl; and

G^1 represents phenyl, quinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, naphthyl, benzofuranyl or benzothienyl, each of which may be optionally substituted with one or two substituents independently selected from methyl, cyano, hydroxyl, oxo, $-CH_2CN$, $-C(O)CF_3$, $-O-SO_2-CH_3$, $-O-CH_2CH_2SO_2CH_3$ and $-O-CH_2CH_2N(CH_3)_2$.

Examples of compounds of the invention include:

(R,R)/(S,S)-5-[(4-(1-Benzothien-2-yl)phenyl)(hydroxy)methyl]-5-methylimidazolidine-2,4-dione,

(*R*,*R*)/(*S*,*S*)-5-[[4-(1-Benzofuran-3-yl)phenyl](hydroxy)methyl]-5-methylimidazolidine-2,4-dione,

(R,R)/(S,S)-5-[Hydroxy(4´-methyl-1,1´-biphenyl-4-yl)methyl]-5-methylimidazolidine-2,4-dione,

(5*R*)-5-[(*R*)-Hydroxy(4-quinoline-6-ylphenyl)methyl]-5-methylimidazolidine-2,4-dione trifluoroacetate,

(R,R)-Methanesulfonic acid 6-{4-[hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-phenyl}-naphthalen-2-yl ester,

(5*R*)-5-[(*R*)-Hydroxy(4-isoquinoline-6-ylphenyl)methyl]-5-methylimidazolidine-2,4-dione trifluoroacetate,

(5*R*)-5-{(*R*)-Hydroxy[4-(6-hydroxy-2-naphthyl)phenyl]methyl}-5-methylimidazolidine-2,4-dione,

(5*R*)-5-[(*R*)-(4-{6-[2-(Dimethylamino)ethoxy]-2-naphthyl}phenyl)(hydroxy)methyl]-5-methylimidazolidine-2,4-dione hydrochloride,

(5*R*)-5-[(*R*)-Hydroxy(4-{6-[2-(methylsulfonyl)ethoxy]-2-naphthyl}phenyl)methyl]-5-methylimidazolidine-2,4-dione,

4'-[(2,5-Dioxoimidazolidin-4-yl)(hydroxy)methyl]-3-methyl-1,1'-biphenyl-4-carbonitrile,

4'-[Hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)methyl]-3-methyl-1,1'-biphenyl-4-carbonitrile,

{4'-[Hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)-1,1'-biphenyl-3-yl}acetonitrile,

5-(Hydroxy{4-[2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoli-6-yl]phenyl}methyl)-5-methylimidazolidine-2,4-dione,

(R,R/S,S)-3-[4-(Biphenyl-4-yl-hydroxy-methyl)-2,5-dioxo-imidazolidin-4-yl]-propionic acid,

(5R)-{[4-(2,2-Dioxo-2,3-dihydro-1H-2lambda*6*-benzo[c]thiophen-5-yl)-phenyl]-(R)-hydroxy-methyl}5-propyl-imidazolidine-2,4-dione,

(5R)-[(R)-Hydroxy-(3'-methyl-biphenyl-4-yl-)-methyl]-5-methyl-imidazolidine-2,4-dione,

and pharmaceutically acceptable salts and solvates thereof.

It will be appreciated that the particular substituents and number of substituents in the compounds of the invention are selected so as to avoid sterically undesirable combinations.

Each exemplified compound represents a particular and independent aspect of the invention.

It will be appreciated that the compounds according to the invention may contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres (chiral centres) in compounds according to the invention can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof. Racemates may be separated into individual optically active forms using known procedures (cf. Advanced Organic Chemistry: 3rd Edition: author J March, p104-107) including for example the formation of diastereomeric derivatives having convenient

optically active auxiliary species followed by separation and then cleavage of the auxiliary species.

Where optically active centres exist in the compounds of the invention, we disclose all individual optically active forms and combinations of these as individual specific embodiments of the invention, as well as their corresponding racemates.

Where tautomers exist in the compounds of the invention, we disclose all individual tautomeric forms and combinations of these as individual specific embodiments of the invention.

The compounds of the invention may be provided as pharmaceutically acceptable salts or solvates. These include acid addition salts such as hydrochloride, hydrobromide, citrate, tosylate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine. Examples of solvates include hydrates.

The compounds of formula (I) have activity as pharmaceuticals. As previously outlined the compounds of the invention are metalloproteinase inhibitors, in particular they are dual inhibitors of MMP12 and MMP9 and may be used in the treatment of diseases or conditions mediated by MMP12 and/or MMP9 such as asthma, rhinitis, chronic obstructive pulmonary diseases (COPD), arthritis (such as rheumatoid arthritis and osteoarthritis), atherosclerosis and restenosis, cancer, invasion and metastasis, diseases involving tissue destruction, loosening of hip joint replacements, periodontal disease, fibrotic disease, infarction and heart disease, liver and renal fibrosis, endometriosis, diseases related to the weakening of the extracellular matrix, heart failure, aortic aneurysms, CNS related diseases such as Alzheimer's disease and Multiple Sclerosis (MS), and hematological disorders.

In the context of the present specification, a compound is considered to be a dual inhibitor of MMP12 and MMP9 if the potency of the compound (as measured by its IC_{50} value) is less than or equal to 100 nanomolar (≤ 100 nm) for each of MMP12 and MMP9, or, if the ratio of the potencies (MMP9:MMP12) is less than or equal to 20 (≤ 20).

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention further provides a method of treating a disease or condition mediated by MMP12 and/or MMP9 which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined.

The invention also provides a method of treating an obstructive airways disease (e.g. asthma or COPD) which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the

disorder indicated. The daily dosage of the compound of formula (I)/salt/solvate (active ingredient) may be in the range from 0.001 mg/kg to 75 mg/kg, in particular from 0.5 mg/kg to 30 mg/kg. This daily dose may be given in divided doses as necessary. Typically unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

The compounds of formula (I) and pharmaceutically acceptable salts and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as hereinbefore defined with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions of this invention may be administered in standard manner for the disease or condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal adminstration or by inhalation. For these

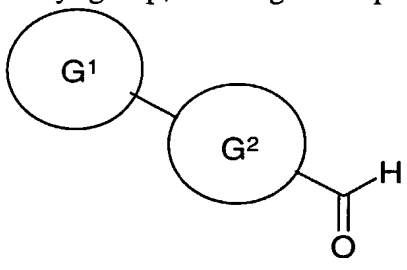
purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solutions or suspensions or sterile emulsions.

In addition to the compounds of the present invention the pharmaceutical composition of this invention may also contain, or be co-administered (simultaneously or sequentially) with, one or more pharmacological agents of value in treating one or more diseases or conditions referred to hereinabove such as "Symbicort" (trade mark) product.

Preparation of the compounds of the invention

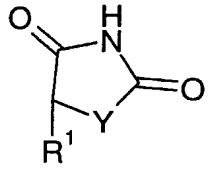
The present invention further provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined above which comprises,

(a) when X represents a hydroxyl group, reacting a compound of formula



(II)

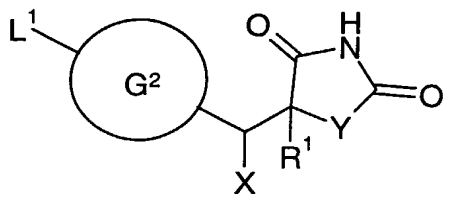
wherein G^1 and G^2 are as defined in formula (I), with a compound of formula



(III)

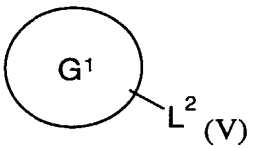
wherein Y and R^1 are as defined in formula (I); or

(b) reacting a compound of formula



(IV)

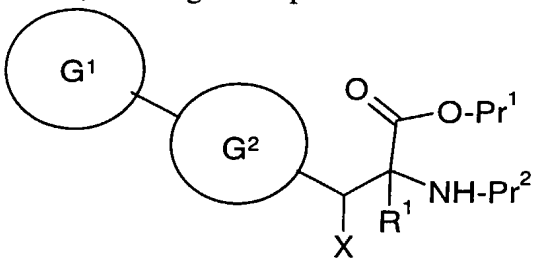
wherein L^1 represents a suitable leaving group (e.g. halogen, triflate, trialkylstannyl, boronic acid or boronic ester) and X, Y, R^1 and G^2 are as defined in formula (I), with a compound of formula



(V)

wherein L^2 represents a suitable leaving group and G^1 is as defined in formula (I) under Suzuki or Stille coupling reaction conditions (for example, as described in *Chem. Rev.*, 1995, 95, 2457-2483 or J.K. Stille, *Angew. Chem. Int. Ed. Engl.*, 25, 508 (1986)); or

(c) when Y represents NH, reacting a compound of formula



(VI)

wherein Pr^1 represents hydrogen or a suitable carboxyl protecting group, Pr^2 represents hydrogen or a suitable amine protecting group and X, R^1, G^1 and G^2 are as defined in formula (I), with an alkali metal or alkaline earth metal cyanate under acidic conditions (e.g. using potassium, sodium or calcium cyanate in the presence of 5M aqueous hydrogen chloride in a solvent such as ethanol and at elevated temperature, for example, from ambient (20°C) to reflux temperature);

and optionally after (a), (b) or (c) forming a pharmaceutically acceptable salt or solvate.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting

reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of the invention may involve, at various stages, the addition and removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 3rd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1999).

Compounds of formulae (II), (III) and (V) are either commercially available, are known in the literature or may be prepared using known techniques.

Compounds of formulae (IV) and (VI) are novel intermediates which form a further aspect of the present invention and which may be prepared using techniques conventional in the art.

The present invention will now be further explained by reference to the following illustrative examples.

General procedures

^{1}HNMR and ^{13}CNMR were recorded on a Varian *unity Inova* 400 MHz or a Varian *Mercury*-VX 300 MHz instrument. The central peaks of chloroform-*d* (δ_H 7.27ppm), dimethylsulfoxide-d_6 (δ_H 2.50 ppm) or methanol-d_4 (δ_H 3.31 ppm) where used as internal references. Low-resolution mass spectra were obtained on an Agilent 100 LC-MS system equipped with an APCI ionisation chamber. Column chromatography was carried out using silica gel (0.063-0.2 mm) (Merck). Unless stated otherwise, starting materials were commercially available. All solvents and commercial reagents were laboratory grade and used as received.

Abbreviations:

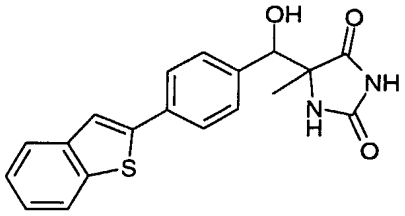
TFA: trifluoroacetic acid

$PdCl_2$ (dppf): bis(diphenylphosphino)ferrocene-palladium(II) chloride dichloromethane complex

EtOH: ethanol

Example 1

(R,R)/(S,S)-5-[(4-(1-Benzothien-2-yl)phenyl)(hydroxy)methyl]-5-methylimidazolidine-2,4-dione



(*R,R*)/(*S,S*)-5-[(4-Iodophenyl)(tetrahydro-2*H*-pyran-2-yloxy)methyl]-5-methylimidazolidine-2,4-dione (0.065 g, 0.15 mmol), benzo[b]thiophene-2-boronic acid (0.039g, 0.22 mmol), toluene (1.8 mL), ethanol (0.20 mL), 2M aqueous sodium carbonate (0.40 mL, 0.80 mmoles) and $PdCl_2$ (dppf) (0.0050 g) were stirred under nitrogen at 90°C (external temperature) for 5 hours. After cooling the solvent was evaporated and the dark residue was taken up in ethyl acetate (5 mL), washed with brine, dried over anhydrous sodium sulfate and concentrated by rotary evaporation. The dark residue was dissolved in dry methanol, gently stirred with "Dowex 50" (trade mark) ion exchange resin (H^+-form) for 8-12 hours until the reaction was complete, filtered and concentrated by rotary evaporation. Purification by reversed-phase HPLC [column: XTerra® Prep MS C_{18} (19x50 mm)] with acetonitrile-water (0.1% TFA) as eluant gave 0.009g of the title compound as a white solid.

^{1}H NMR 400 MHz (DMSO-d_6): δ 1.42 (s, 3H), 4.65 (s, 1H), 6.04 (br s, 1H), 7.32-7.40 (2H), 7.37 (d, 2H, *J*= 8.4 Hz), 7.69 (d, 2H, *J*= 8.4 Hz), 7.82 (d, 1H, *J*= 8.0 Hz), 7.86 (s, 1H), 7.95 (d, 1H, *J*= 8.0 Hz), 8.15 (br s, 1H) and 10.2 (br s, 1H).

LC-MS (APCI) m/z = 353.1 (MH^+).

Preparation of starting materials:

(*R,R*)/(*S,S*)-5-[(4-Iodophenyl)(tetrahydro-2*H*-pyran-2-yloxy)methyl]-5-methylimidazolidine-2,4-dione

4-Iodobenzaldehyde (9.28 g, 40 mmol), 5-methylhydantoin (4.56 g, 40 mmol) and 45% aqueous trimethylamine (6.40 mL, 40 mmol) were refluxed in ethanol (60 mL) and water (40 mL) for 20 hours under an atmosphere of nitrogen. After cooling at 23°C for 15 minutes the white precipitate was collected by filtration, washed repeatedly with 50% ethanol in water (50mL), water (50 mL), and diethyl ether (50 mL). Drying by air suction afforded 8.0 g (58% yield) of a mixture of (*R,R*)/(*S,S*)-5-[hydroxy(4-iodophenyl)methyl]-5-methylimidazolidine-2,4-dione as a white solid.

^{1}H NMR 300MHz (DMSO-d_6): δ 1.40 (s, 3H), 4.57 (d, 1H, *J*= 4.2 Hz), 5.97 (d, 1H, *J*= 4.2 Hz), 7.07 (d, 2H, *J*= 8.4 Hz), 7.64 (d, 2H, *J*= 8.4 Hz), 8.08 (s, 1H) and 10.2 (br s, 1H). LC-MS (APCI) m/z 347.1 (MH^+).

The racemate from above (1.7 g, 5.0 mmol), 3,4-dihydro-2*H*-pyran (1.8 mL, 20 mmol), pyridinium 4-toluenesulfonate (0.52 g, 2 mmol) and dry tetrahydrofuran (50 mL) were stirred at 23°C for 96 hours. The white solid was filtered off and the clear filtrate was concentrated with silica (25 g) by rotary evaporation until dryness. The product thus obtained was applied on a silica column. Elution with ethyl acetate/n-heptane (1:3) through (2:1) afforded 2.1 g (99% yield) of (*R,R*)/(*S,S*)-5-[(4-iodophenyl)(tetrahydro-2*H*-pyran-2-yloxy)methyl]-5-methylimidazolidine-2,4-dione as a mixture of the diastereomeric pairs.

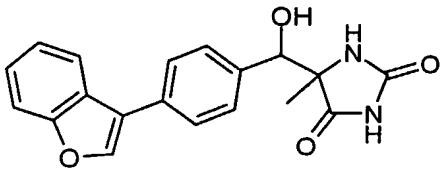
^{1}H NMR 300MHz (DMSO-d_6): δ 1.32-1.83 6H), 1.34 (s, 1.4H), 1.44 (s, 1.6H), 3.09-3.88 (2H), 4.26 (m, 0.54H), 4.54 (s, 0.46H), 4.66 (s, 0.54H), 4.81 (m, 0.46H), 7.03 (d, 1.1H, *J*=

8.4 Hz), 7.08 (d, 0.90H, *J*= 8.4 Hz), 7.66 (d, 0.90H, *J*= 8.4 Hz), 7.70 (d, 1.1H, *J*= 8.4 Hz), 8.18 (s, 0.48H), 8.28 (s, 0.52H) and 10.3 (br s, 1H).

The following racemic compounds were prepared by methods analogous to the method described in Example 1 above.

Example 2

(*R,R*)/(*S,S*)-5-[[4-(1-Benzofuran-3-yl)phenyl](hydroxy)methyl]-5-methylimidazolidine-2,4-dione

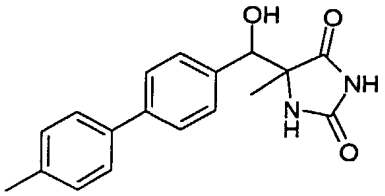


From (*R,R*)/(*S,S*)-5-[(4-iodophenyl)(tetrahydro-2*H*-pyran-2-yloxy)methyl]-5-methylimidazolidine-2,4-dione (0.065 g, 0.15 mmoles) and 3-benzofuranboronic acid (0.036 g, 0.22 mmoles). Yield: 0.010 g (20% yield) of a white solid.

^{1}H-NMR 400 MHz (DMSO-d_6) δ 1.44 (s, 3H), 4.68 (d, 1H, *J*= 4.0 Hz), 6.00 (d, 1H, *J*= 4.0 Hz), 7.26 (dt, 1H, J_1= 1.6 Hz, J_2= 7.2 Hz), 7.32 (dt, 1H, J_1= 1.6 Hz, J_2= 7.2 Hz), 7.40 (d, 2H, *J*= 8.0 Hz), 7.42 (d, 1H, *J*= 0.8 Hz), 7.62 (d, 1H, *J*= 8.0 Hz), 7.65 (d, 1H, *J*= 7.6 Hz), 7.83 (d, 2H, *J*= 8.0 Hz), 8.12 (s, 1H) and 10.2 (br s, 1H) ppm.
LC-MS (APCI) m/z = 337.4 (MH^+).

Example 3

(R,R)/(S,S)-5-[Hydroxy(4´-methyl-1,1´-biphenyl-4-yl)methyl]-5-methylimidazolidine-2,4-dione

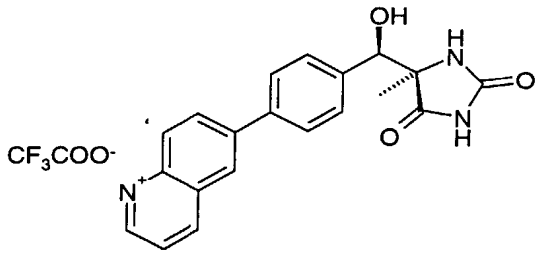


The title compound was prepared from (*R,R*)/(*S,S*)-5-[(4-iodophenyl)(tetrahydro-2*H*-pyran-2-yloxy)methyl]-5-methylimidazolidine-2,4-dione (0.065 g, 0.15 mmol) and 4-methylphenylboronic acid (0.030 g, 0.22 mmol). Yield: 0.020 g of a white solid.

^{1}H NMR 400 MHz (DMSO-d_6): δ 1.43 (s, 3H), 2.33 (s, 3H), 4.65 (s, 1H), 5.93 (br s, 1H), 7.25 (d, 2H, *J*= 8.8 Hz), 7.34 (d, 2H, *J*= 8.8 Hz), 7.55 (d, 2H, *J*= 8.4 Hz), 7.56 (d, 2H, *J*= 8.4 Hz), 8.11 (s, 1H) and 10.2 (br s, 1H).
LC-MS (APCI) m/z = 311.4 (MH^+).

Example 4

(5*R*)-5-[(*R*)-Hydroxy(4-quinoline-6-ylphenyl)methyl]-5-methylimidazolidine-2,4-dione trifluoroacetate



(5*R*)-5-{(*R*)-(4-Iodophenyl)[(2*R*)-tetrahydro-2*H*-pyran-2-yloxy]methyl}-5-methylimidazolidine-2,4-dione (0.087 g, 0.202 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (0.077 g, 0.30 mmol), ethanol (0.30 mL), toluene (2.7 mL), 2M aqueous sodium carbonate (0.54 mL, 1.1 mmol) and $PdCl_2$ (dppf) (0.0060 g) were stirred under nitrogen at 89°C (external temperature) for five hours. After cooling the solvent was evaporated and the dark residue was taken up in ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated by rotary evaporation to give 0.16 g of an impure product. Purification by reversed- phase HPLC ["Chromasil" (trade mark) C_{18} column (20mm I.D x 250 mm L)] using acetonitrile-water (0.1% TFA added) as eluant gave 0.014 g of the title compound as a white solid. Due to the acid present in the eluant the protective group was cleaved off on concentration of the fractions containing target compound.

^{1}H NMR 400 MHz (CD_3OD): δ 1.63 (s, 3H), 4.87 (s, 1H), 7.56 (d, 2H, J= 8.4 Hz), 7.79 (d, 2H, *J*= 8.4 Hz), 7.87 (m, 1H), 8.22 (m, 1H), 8.33 (m, 1H), 8.41 (m, 1H), 8.89 (m, 1H) and 9.04 (m, 1H).

LC-MS (APCI) m/z = 348.3 (MH^+):

Preparation of starting materials:

(5*R*)-5-{(*R*)-(4-Iodophenyl)[(2*R*)-tetrahydro-2*H*-pyran-2-yloxy]methyl}-5-methylimidazolidine-2,4-dione

(*R,R*)/(*S,S*)-5-[(4-iodophenyl)(tetrahydro-2*H*-pyran-2-yloxy)methyl]-5-methylimidazolidine-2,4-dione (0.23g) prepared as described in Example 1 above was dissolved in absolute ethanol (15 mL) and injected repeatedly (3x5 mL) on a chiral column ["Chiralpak" (trade mark) AD-H column (2 cm I.D x 25 cm length)] connected to a UV-detector (254 nm) and a fraction collector. Separation was performed with iso-hexane/absolute ethanol (1:1) at 8.0 mL/min flow and the pure enantiomers eluted after 15, 18, 21 and 35 minutes, respectively. The titled compound was the third isomer to be eluted (Yield: 0.045 g of a colourless oil that turned solid on standing).

^{1}H NMR 300 MHz (DMSO-d_6): δ 1.34 (s, 3H), 1.32-1.83 (6H), 3.13 (m, 1H), 3.30 (m, 1H), 4.54 (s, 1H), 4.81 (m, 1H), 7.08 (d, 2H, *J*= 8.4 Hz), 7.66 (d, 2H, *J*= 8.4 Hz), 8.18 (s, 1H), 10.4 (br s, 1H).

Chiral chromatography ["Chiralpak" (trade mark) column AD-H (0.45 cm I.D x 25 cm L) at 0.48 mL/min iso-hexane/absolute ethanol (1:1)].

Retention time (at peak maximum): 15.2 minutes

Optical purity: >99.9% e.e

6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline

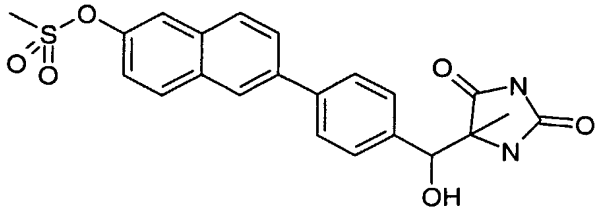
6-Bromoquinoline (0.98 g, 4.6 mmol), bis(pinacolato)diboron (1.3 g, 5.2 mmol), $PdCl_2$ (dppf) (0.10 g, 0.14 mmol), potassium acetate (1.4 g, 14 mmol) and dry *N,N*-dimethylformamide (28 mL) were stirred under nitrogen at 80°C (internal temperature) for six hours. The solvent was evaporated, the residue taken up in ethyl acetate (80 mL) and filtered through Celite® filter aid. The clear filtrate was concentrated with silica (10 g) by rotary evaporation until dryness and the product thus obtained was applied on a silica column. Elution with ethyl acetate/n-heptane (1:3) through (2:1) and ethyl acetate (neat) gave 0.54 g (45% yield) of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline as a colourless oil that crystallised in the cold.

^{1}H NMR 400 MHz ($CDCl_3$): δ 1.40 (s, 12H), 7.41 (dd, 1H, J_1= 4.4 Hz, J_2= 8.4 Hz), 8.090 (s, 1H), 8.092 (s, 1H), 8.20 (dd, 1H, J_1= 1.7 Hz, J_2= 8.4 Hz), 8.35 (s, 1H) and 8.95 (dd, 1H, J_1= 1.8 Hz, J_2= 4.4 Hz).

The following compounds were prepared by methods analogous to the method described in Example 4 above.

Example 5

(R,R)-Methanesulfonic acid 6-{4-[hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-phenyl}-naphthalen-2-yl ester



Prepared from methanesulfonic acid 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaboralan-2-yl)-naphthalen-2-yl ester and (*R,R*)/(*S,S*)-5-[(4-Iodophenyl)(tetrahydro-2*H*-pyran-2-yloxy)methyl]-5-methylimidazolidine-2,4-dione in 2 % yield.

^{1}HNMR 300 MHz (DMSO-d_6): δ 1.46 (s, 3H), 3.46 (s, 3H), 4.70 (d, 1H), 5.98 (d, 1H), 7.43 (d, 2H), 7.52 (dd, 1H), 7.77 (d, 2H), 7.93-7-97 (m, 2H), 8.06-8.14 (m, 3H), 8.32 (s, 1H), 10.21 (s, 1H).

LC-MS (APCI) m/z = 441.1 (MH^+)

Preparation of starting materials:

Methanesulfonic acid 6-bromo-naphthalen-2-yl-ester

Methanesulfonyl chloride (0.400 ml, 5.15 mmol) was added to a solution of 6-bromo-2-naphthol (1.101 g, 4.94 mmol) and triethylamine (0.700 ml, 5.02 mmol) in dichloromethane (4 Å molecular sieve dried, 10 ml). After 30 minutes the reaction was quenched by addition of water (20 ml) and dichloromethane (30 ml). The organic phase was evaporated to afford 1.459 g of the title compound as a white solid in 98.1 % yield.

^{1}HNMR 300 MHz (DMSO-d_6): δ 3.46 (s, 3H), 7.56 (dd, 1H), 7.73 (dd, 1H), 7.98 (d, 1H), 7.98 (d, 1H), 8.05 (d, 1H), 8.31(d, 1H).

Methanesulfonic acid 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaboralan-2-yl)-naphthalen-2-yl ester

Potassium acetate (620 mg, 6.32mol), methanesulfonic acid 6-bromo-naphthalen-2-yl-ester (603 mg, 2.0 mmol), bis(pinacolato)diboron (569 mg, 2.24 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloro-palladium(II) complex with dichloromethane (1:1) (56.8 mg, 0.07 mmol) was stirred with a stream of nitrogen for 30 minutes. Dioxane (4 Å molecular sieve dried, 15 ml) was added. The slurry was deoxygenated three times (vacuum followed by nitrogen atmosphere) with the help of a manifold. The slurry was then heated to 100°C for 90 minutes with nitrogen as a protective gas. Water (50 ml) was added, followed by ethyl acetate (50 ml) and diethylether 850 ml). The organic phase was filtered through a small column of silica.

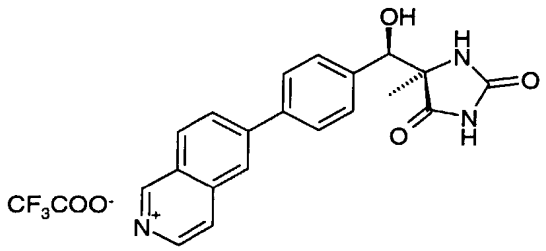
Elution of the silica with a mixture of ethyl acetate and heptane 2:1 (100 ml) and evaporation afforded 671 mg of the title compound in 96.4 % yield as a brownish oil.

^{1}HNMR 300 MHz (DMSO-d_6): δ 1.34 (s, 12H), 3.46 (s, 3H), 7.51 (dd, 1H), 7.78 (dd, 1H), 7.94 (d, 1H), 7.98 (d, 1H), 8.17 (d, 1H), 8.39 (s, 1H).

LC-MS (APCI) m/z = 348.3 (MH^+)

Example 6

(5*R*)-5-[(*R*)-Hydroxy(4-isoquinoline-6-ylphenyl)methyl]-5-methylimidazolidine-2,4-dione trifluoroacetate



The title compound was prepared from (5*R*)-5-{(*R*)-(4-iodophenyl)[(2*R*)-tetrahydro-2*H*-pyran-2-yloxy]methyl}-5-methylimidazolidine-2,4-dione (0.087 g, 0.202 mmol) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline (0.077 g, 0.30 mmol). Yield: 0.003 g of a white solid.

^{1}H NMR 400 MHz (CD_3OD): δ 1.63 (s, 3H), 4.88 (s, 1H), 7.57 (d, 2H, J= 8.4 Hz), 7.83 (d, 2H, *J*= 8.4 Hz), 8.17-8.45 (4H), 8.55 (br m, 1H) and 9.56 (br m, 1H).

LC-MS (APCI) m/z 348.1 (MH^+).

Preparation of starting materials:

6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline

The title compound was prepared in 34% yield using 6-bromoisoquinoline (1.10 g, 5.3 mmol) according to the procedure described above for 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (see Example 4).

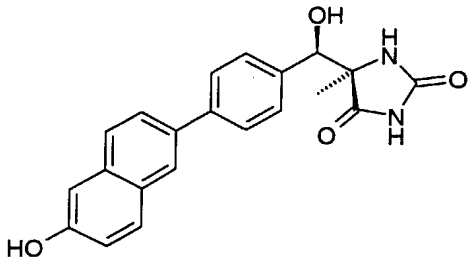
^{1}H NMR 400 MHz ($CDCl_3$): δ 1.39 (s, 12H), 7.68 (d, 1H, *J*= 6.0 Hz), 7.96 (m, 2H), 8.34 (s, 1H), 8.53 (d, 1H, *J*= 6.4 Hz) and 9.26 (s, 1H).

6-Bromoisoquinoline

The title compound was prepared in 10% yield according to method described by Nerenz *et al. J. Chem. Soc.*, Perkin Transactions 2, 1998, 437-448.

Example 7

(5*R*)-5-{(*R*)-Hydroxy[4-(6-hydroxy-2-naphthyl)phenyl]methyl}-5-methylimidazolidine-2,4-dione



The title compound was prepared from (5*R*)-5-{(*R*)-(4-iodophenyl)[(2*R*)-tetrahydro-2*H*-pyran-2-yloxy]methyl}-5-methylimidazolidine-2,4-dione (0.087 g, 0.202 mmol) and 2-{[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthyl]oxy}tetrahydro-2*H*-pyran (0.077g, 0.30 mmol). Yield: 0.026 g of a white solid.

^{1}H NMR 400 MHz (DMSO-d_6): δ 1.45 (s, 3H), 4.67 (s, 1H), 5.96 (br s, 1H), 7.09-7.14 (2H), 7.38 (d, 2H, *J*= 8.4 Hz), 7.69 (d, 2H, *J*= 8.4 Hz), 7.70-7.77 (2H), 7.83 (d, 1H, *J*= 8.8 Hz), 8.08 (s, 1H), 8.14 (br s, 1H), 9.88 (br s, 1H) and 10.2 (br s, 1H).

LC-MS (APCI) m/z = 363.1 (MH^+).

Preparation of starting materials:

2-{[6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthyl]oxy}tetrahydro-2*H*-pyran

The title compound was prepared in 61% yield as a white crystalline solid from 2-[(6-bromo-2-naphthyl)oxy]tetrahydro-2*H*-pyran (0.71 g, 2.2 mmol) according to the procedure described above for 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline (see Example 4).

^{1}H NMR 400 MHz ($CDCl_3$): δ 1.38 (s, 12H), 1.58-2.13 (6H), 3.65 (m, 1H), 3.94 (m, 1H), 5.58 (m, 1H), 7.22 (dd, 1H, J_1= 2.4 Hz, J_2= 8.8 Hz), 7.40 (d, 1H, J= 2.4 Hz), 7.71 (d, 1H, J= 8.4 Hz), 7.78 (dd, 1H, J_1= 1.2 Hz, J_2= 8.4 Hz), 7.79 (d, 1H, J= 8.8 Hz) and 8.28 (s, 1H).

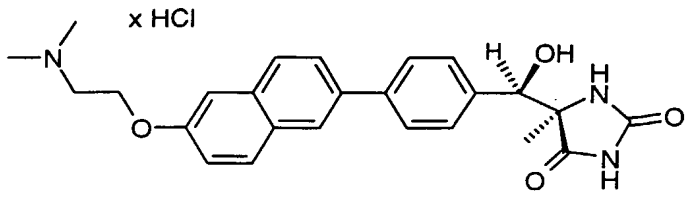
2-[(6-Bromo-2-naphthyl)oxy]tetrahydro-2*H*-pyran

6-Bromo-2-naphthol (1.05 g, 4.6 mmol), 3,4-dihydro-2*H*-pyran (5.0 mL, 55 mmol), pyridinium 4-toluenesulfonate (0.047 g) and dry dichloromethane (15 mL) were stirred under nitrogen at 23°C for 3.5 hours and concentrated by rotary evaporation until dryness. The white solid was triturated with ethyl acetate (40 mL) and the extract was concentrated with silica (10 g) and applied on a silica column. Elution with ethyl acetate/n-heptane (1:6) gave 1.33 g (92% yield) of the title compound as a white solid.

^{1}H NMR 400MHz ($CDCl_3$): δ 1.58-2.12 (6H), 3.65 (m, 1H), 3.93 (m, 1H), 5.56 (t, 1H, 3.2 Hz), 7.25 (dd, 1H, J_1= 2.9 Hz, J_2= 8.8 Hz), 7.39 (d, 1H, J= 2.9 Hz), 7.48 (dd, 1H, J_1= 2.0 Hz, J_2= 8.8 Hz), 7.60 (d, 1H, J= 8.8 Hz), 7.66 (d, 1H, J= 8.8 Hz) and 7.92 (d, 1H, J= 2.0 Hz).

Example 8

(5*R*)-5-[(*R*)-(4-{6-[2-(Dimethylamino)ethoxy]-2-naphthyl}phenyl)(hydroxy)methyl]-5-methylimidazolidine-2,4-dione hydrochloride



The title compound was prepared from (5*R*)-5-{(*R*)-(4-iodophenyl)[(2*R*)-tetrahydro-2*H*-pyran-2-yloxy]methyl}-5-methylimidazolidine-2,4-dione as described in Example 4 (0.047 g, 0.11 mmoles) and *N*,*N*-dimethyl-*N*-(2-{[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthyl]oxy}ethyl)amine (0.056 g, 0.16 mmoles). The crude product was treated with 1.5% conc. HCl in methanol (20 mL) for 3.5 hours at room temperature, concentrated and purified by reversed-phase HPLC. Yield: 0.043 g (83% yield) of a white solid.

^{1}H-NMR 400 MHz (CD_3OD) δ 1.62 (s, 3H), 3.00 (s, 6H), 3.65 (t, 2H, *J*= 4.9 Hz), 4.46 (t, 2H, *J*= 4.9 Hz), 7.23 (dd, 1H, J_1= 2.7 Hz, J_2= 8.8 Hz), 7.33 (d, 1H, *J*= 2.7 Hz), 7.48 (d, 2H, *J*= 8.0 Hz), 7.65 (d, 2H, *J*= 8.0 Hz), 7.71 (dd, 1H, J_1= 1.6 Hz, J_2= 8.6 Hz), 7.826 (d, 1H, *J*= 8.6 Hz), 7.838 (d, 1H, *J*= 8.8 Hz) and 7.99 (br s, 1H) ppm.
LC-MS (APCI) m/z = 434.2 (MH^+).

Preparation of starting materials:

N,*N*-Dimethyl-*N*-(2-{[6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthyl]oxy}ethyl)amine

N-{2-[(6-Bromo-2-naphthyl)oxy]ethyl}-*N*,*N*-dimethylamine (0.30 g, 1.0 mmol), 4,4,5,5-tetramethyl[1,3,2]dioxaborolane (0.22 mL, 1.5 mmoles), $PdCl_2$(dppf) xCH_2Cl_2 (0.024 g, 0.030 mmoles), triethylamine (0.42 mL, 3.0 mmoles), anhydrous dioxane (4.0 mL) were stirred under argon at 100°C (internal temperature) overnight. The solvent was evaporated, the residue taken up in ethyl acetate (80 mL) and filtered through Celite® filter aid. The clear filtrate was concentrated by rotary evaporation until dryness and the residue was

applied on a silica column. Elution with neat tetrahydrofuran (distilled prior to use) gave 0.115 g (33% yield) of the title compound as a white solid.

^{1}H-NMR 400 MHz ($CDCl_3$) δ 1.38 (s, 12H), 2.38 (s, 6H), 2.82 (t, 2H, *J*= 5.7 Hz), 4.20 (t, 2H, *J*= 5.7 Hz), 7.124 (d, 1H, *J*= 2.5 Hz), 7.165 (dd, 1H, J_1= 2.7 Hz, J_2= 9.0 Hz), 7.70 (d, 1H, *J*= 8.2 Hz), 7.77 (d, 1H, *J*= 9.0 Hz), 7.79 (dd, 1H, J_1= 1.1 Hz, J_2= 8.2 Hz) and 8.28 (br s, 1H) ppm.
LC-MS (APCI) m/z = 342.3 (MH^+).

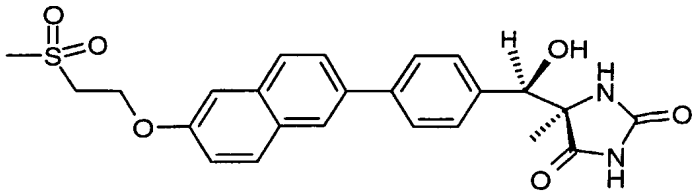
N-{2-[(6-Bromo-2-naphthyl)oxy]ethyl}-*N*,*N*-dimethylamine

The title compound was prepared from 6-bromo-2-naphthol (1.14 g, 5.0 mmoles) and 2-(dimethylamino)ethyl chloride hydrochloride (1.66 g, 11.5 mmoles) by analogy with the method described by Meegan *et al.*, *J. Med. Chem.*, 2001, 44, 1072-1084. Reflux for 25 hours under nitrogen, work-up and purification by reverse-phase HPLC ["Chromasil" (trade mark) C_{18} column (50 mm I.D x 250 mm L)] using acetonitrile-water (0.1% TFA added) as eluant gave 1.94 g of the trifluoroacetic acid salt. Treatment with excess aqueous sodium carbonate solution, extraction with ethyl acetate (3x100 mL), drying of the organic extracts over anhydrous sodium sulfate and concentration by rotary evaporation gave 1.12 g (75% yield) of the title compound as an off-white solid.

^{1}H-NMR 400 MHz ($CDCl_3$) δ 2.38 (s, 6H), 2.80 (t, 2H, *J*= 5.7 Hz), 4.18 (t, 2H, *J*= 5.7 Hz), 7.10 (d, 1H, *J*= 2.5 Hz), 7.20 (dd, 1H, J_1= 2.5 Hz, J_2= 8.9 Hz), 7.49 (dd, 1H, J_1= 2.0 Hz, J_2= 8.8 Hz), 7.59 (d, 1H, *J*= 9.0 Hz), 7.64 (d, 1H, *J*= 9.0 Hz) and 7.91 (d, 1H, *J*= 2.0 Hz) ppm.
LC-MS (APCI) m/z = 294.1and 296.1 (MH^+).

Example 9

(5*R*)-5-[(*R*)-Hydroxy(4-{6-[2-(methylsulfonyl)ethoxy]-2-naphthyl}phenyl)methyl]-5-methylimidazolidine-2,4-dione



The title compound was prepared from (5*R*)-5-{(*R*)-(4-iodophenyl)[(2*R*)-tetrahydro-2*H*-pyran-2-yloxy]methyl}-5-methylimidazolidine-2,4-dione as described in Example 4 (0.042g, 0.098 mmoles) and 4,4,5,5-tetramethyl-2-{6-[2-(methylthio)ethoxy]-2-naphthyl}-1,3,2-dioxaborolane (0.044 g, 0.13 mmoles). Stirring at 90°C overnight, followed by aqueous work-up and chromatography on silica with ethyl acetate -heptanes (1:5) through (2:1) afforded 0.041 g of (5*R*)-5-methyl-5-{(*R*)-(4-{6-[2-(methylthio)ethoxy]-2-naphthyl}phenyl)[(2*R*)-tetrahydro-2*H*-pyran-2-yloxy]methyl}imidazolidine-2,4-dione. This product was stirred with m-chloroperbenzoic acid (77%, 0.030 g), saturated aqueous sodium bicarbonate (2.0 mL) and dichloromethane (2.5 mL) for 1.5 hours at room temperature. Dimethylsulfide (3-4 drops) was added and after stirring for another five minutes, the solution was taken up in ethyl acetate, washed with water, brine and dried over anhydrous sodium sulfate. The solution was filtered, concentrated by rotary evaporation and subsequently treated with 1.5% conc. hydrochloric acid in methanol (12 mL) for 15 hours at room temperature. The mixture was then concentrated until dryness and the crude product thus obtained was purified by reverse-phase HPLC. Yield: 0.013 g (28% overall yield) of a white solid.

^{1}H-NMR 400 MHz (DMSO-d_6) δ 1.45 (s, 3H), 3.12 (s, 3H), 3.71 (t, 2H, J= 5.8 Hz), 4.50 (t, 2H, J= 5.8 Hz), 4.68 (d, 1H, J= 3.7 Hz), 5.95 (d, 1H, J= 4.0 Hz), 7.23 (dd, 1H, J_1= 2.5 Hz, J_2= 8.9 Hz), 7.40 (d, 2H, J= 8.4 Hz), 7.44 (d, 1H, J= 2.4 Hz), 7.72 (d, 2H, J= 8.5 Hz), 7.82 (dd, 1H, J_1= 1.7 Hz, J_2= 8.5 Hz), 7.91 (d, 1H, J= 10.1 Hz), 7.93 (d, 1H, J= 10.1 Hz), 8.13 (s, 1H), 8.17 (br s, 1H) and 10.1 (br s, 1H) ppm.

LC-MS (APCI) m/z = 469.2 (MH^+) and 492.3 (MNa^+).

Preparation of starting materials:

4,4,5,5-Tetramethyl-2-{6-[2-(methylthio)ethoxy]-2-naphthyl}-1,3,2-dioxaborolane

2-Bromo-6-[2-(methylthio)ethoxy]naphthalene (1.2 g, 4.2 mmoles), bis(pinacolato)diboron (1.2 g, 4.6 mmoles), $PdCl_2$ (dppf) xCH_2Cl_2 (0.092 g, 0.11 mmoles), potassium acetate (1.2 g, 13 mmoles) and anhydrous *N*,*N*-dimethylformamide (24 mL) were stirred under argon at 90°C (internal temperature) for seven hours. The reaction was left overnight at ambient temperature. The salts were filtered off, washed with dioxane and the combined filtrates were concentrated to dryness. The solid residue was dissolved in ethyl acetate (100 mL), concentrated with silica (30 g) and applied on a silica column. Elution with ethyl acetate-heptanes (1:20) through (1:15) gave the title compound. Yield: 0.91 g (63% yield) of a white solid.

^{1}H-NMR 400 MHz ($CDCl_3$) δ 1.38 (s, 12H), 2.25 (s, 3H), 2.95 (t, 2H, J= 7.0 Hz), 4.29 (t, 2H, J= 6.8 Hz), 7.12 (br s, 1H), 7.14 (dd, 1H, J_1= 2.6 Hz, J_2= 8.2 Hz), 7.70 (d, 1H, J= 8.2 Hz), 7.78 (d, 1H, J= 9.6 Hz), 7.80 (dd, 1H, J_1= 1.2 Hz, J_2= 8.4 Hz) and 8.28 (br s, 1H) ppm. LC-MS (ES) m/z = 367.3 (MNa^+).

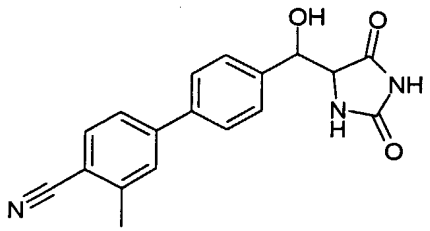
2-Bromo-6-[2-(methylthio)ethoxy]naphthalene

6-Bromo-2-naphthol (1.2 g, 5.0 mmoles), chloroethyl methyl sulfide (0.51 mL, 5.0 mmoles), anhydrous potassium carbonate (0.83 g, 6.0 mmoles), potassium iodide (0.083 g, 0.50 mmoles) and dry acetonitrile (6.5 mL) were stirred under an atmosphere of nitrogen at 50°C (oil bath temperature) for five hours. More chloroethyl methyl sulfide (0.10 mL, 1.0 mmoles) was added and stirring continued at 56°C (oil bath temperature) for 24 hours. The salts were filtered off, washed with acetonitrile and the combined filtrates were concentrated. The residue was triturated with aliquots of ethyl acetate and the washings were concentrated to give an oil. Chromatography on silica with ethyl acetate-heptanes (1:20) as eluant gave the title compound as a colourless oil that solidified on standing. Yield: 1.30 g (87% yield).

^{1}H-NMR 400 MHz ($CDCl_3$) δ 2.25 (s, 3H), 2.95 (t, 2H, *J*= 6.8 Hz), 4.27 (t, 2H, *J*= 6.7 Hz), 7.10 (d, 1H, *J*= 2.5 Hz), 7.17 (dd, 1H, J_1= 2.5 Hz, J_2= 8.9 Hz), 7.50 (dd, 1H, J_1= 2.0 Hz, J_2= 8.7 Hz), 7.59 (d, 1H, *J*= 8.7 Hz), 7.65 (d, 1H, *J*= 8.7 Hz) and 7.92 (d, 1H, *J*= 2.0 Hz) ppm.
LC-MS (APCI) m/z = 296.5/298.3 (MH^+), 313.2/315.0 (M+17).

Example 10

4'-[(2,5-Dioxoimidazolidin-4-yl)(hydroxy)methyl]-3-methyl-1,1'-biphenyl-4-carbonitrile



4'-Formyl-3-methyl-1-1'-biphenyl-4-carbonitrile (0.265g, 1.19mmol), hydantoin (0.179g, 1.19 mmol) and trimethylamine (45% in water, 410 µl) in EtOH (5 ml) and water (1ml) was stirred at 80^{0}C for 40 minutes in a microwave at 300 Watts. The isomeric mixture was separated with HPLC on a "Chromasil" (trade mark) C_{18} column, and the enantiomers were separated on a "Chiralpak" (trade mark) AD column affording one isolated enantiomer in 4% yield.

^{1}H NMR 400 MHz (DMSO-d_6): δ 10.31 (1H, s); 8.06 (1H, s); 7.81 (2H, d, *J*=8.20Hz); 7.79 (1H, s); 7.68 (3H, m); 7.41 (2H, d, *J*=8.20Hz); 5.94 (1H, d, *J*=3.43Hz); 4.96 (1H, s); 4.37 (1H, s) 2.54 (3H, s).

Preparation of starting materials:

4'-Formyl-3-methyl1-1'-biphenyl-4-carbonitrile

A mixture of 4-formylphenylboronic acid (0.677g, 4.5 mmol), 4-bromo-2-methylbenzonitrile (0.59g, 0.3.0mmol), 1.08g (12 mmol) of powdered sodium

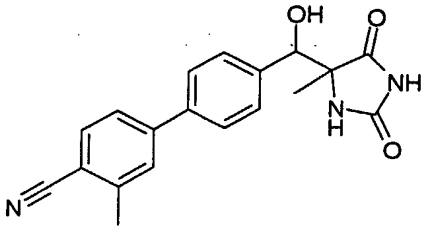
hydrogencarbonate ($NaHCO_3$) in dioxane (10 ml) and water (10 ml) was flushed with argon, energetically stirred and degassed to remove oxygen (O_2). 30 mg of palladium acetate ($Pd(OAc)_2$) was added and the mixture was stirred and heated for 2 hours at 80^0C under argon. The reaction mixture was cooled to room temperature, filtrated and the solvents were removed to give a crude product. Preparative HPLC on a "Chromasil" (trade mark) C_{18} column with acetonitrile/water (0.1% trifluoroacetic acid) afforded 300mg (45% yield) of the title compound.

^{1}H NMR 400MHz ($CDCl_3$): δ 10.11 (1H, s); 8.01 (2H, d, *J*=8.20Hz); 7.77 (2H, d, *J*=8.20Hz); 7.73 (1H, d, *J*=8.01); 7.60 (1H, s);7.55 (1H, d, *J*=8.20Hz) 2.66 (3H, s). API-ES m/z = 222.2 (MH^+).

The following compounds were prepared by methods analogous to the method described in Example 10 above.

Example 11

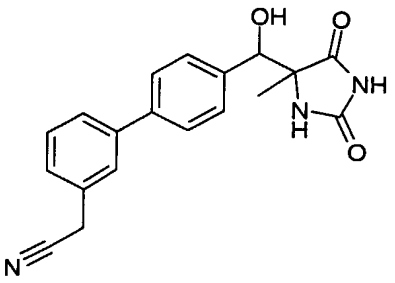
4'-[Hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)methyl]-3-methyl-1,1'-biphenyl-4-carbonitrile



^{1}H NMR 400 MHz (DMSO-d_6): δ 10.31 (1H, s); 8.06 (1H, s); 7.81 (2H, d, *J*=8.20Hz); 7.79 (1H, s); 7.68 (3H, m); 7.41 (2H, d, *J*=8.20Hz); 5.94 (1H, d, *J*=3.43Hz); 4.37 (1H, s) 2.54 (3H, s); 1.41 (1H, s).

Example 12

{4'-[Hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)-1,1'-biphenyl-3-yl}acetonitrile

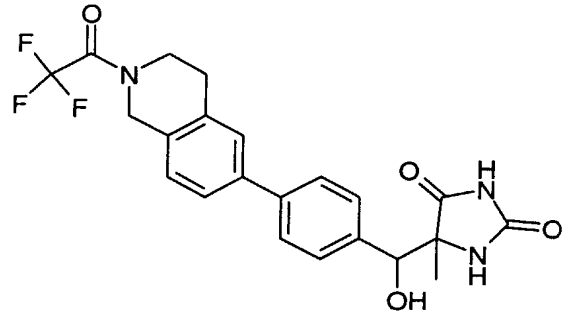


^{1}H NMR 400 MHz (DMSO-d_6): δ 10.16 (1H, s); 8.09 (1H, s); 7.59 (4H, m); 7.47 (1H, s); 7.36 (3H, m); 5.92 (1H, d, *J*=4.58Hz); 4.65 (1H, d, *J*=4.39Hz); 4.08 (2H,s); 1.42, (3H,s).

LC-MS (APCI) m/z = 336.1 (MH^+).

Example 13

5-(Hydroxy{4-[2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoli-6-yl]phenyl}methyl)-5-methylimidazolidine-2,4-dione



^{1}H NMR (300 MHz, DMSO-d_6): δ 1.44 (s, 3H), 2.99 (m, 2H), 3.85(m, 2H), 4.66 (m, 1H), 4.78 (m, 2H), 5.91 (m, 1H), 7.69-7.30 (b, 7H), 8.11 (s, 1H), 10.19 (s, 1H).

LC-MS (APCI) m/z: 448.3 [MH^+]

Preparation of starting materials:

6-Bromo-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline

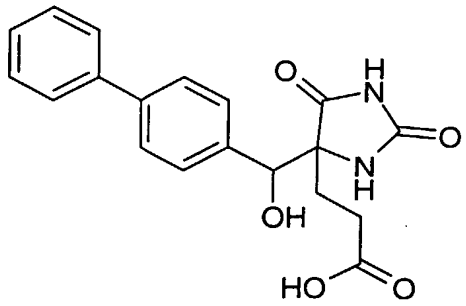
The title compound was prepared as described by G.E.Stoker, *Tetrahedron Lett*, Vol 37, No. 31, pp5453-5456, 1996.

4-[2-(Trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzaldehyde

The title compound was prepared by a Suzuki coupling between 6-bromo-2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoline and 4-formylphenylboronic acid according to conditions described for the synthesis of 4'-formyl-3-methyl-1,1'-biphenyl-4-carbonitrile in Example 10 above.

Example 14

(R,R/S,S)-3-[4-(Biphenyl-4-yl-hydroxy-methyl)-2,5-dioxo-imidazolidin-4-yl]-propionic acid



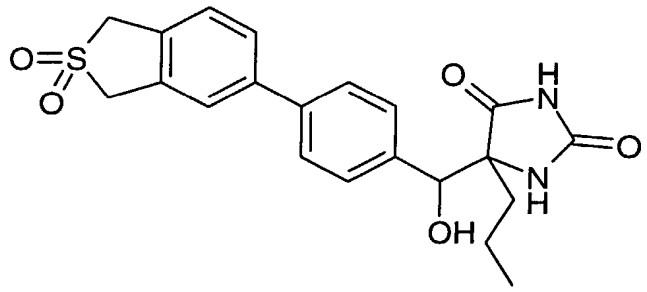
4-Biphenyl-carboxaldehyde (180 mg, 1 mmol), 3-(2,5-dioxo-imidazolidin-4-yl)-propionic acid (180 mg, 1 mmol, Beilstein registry number 83925) and trimethylamine (60% aqueous solution, 0.350 ml) dissolved in ethanol (4 ml) and water (1 ml) was stirred at 80 °C for 16 hours. Evaporation and purification by reverse-phase HPLC ("Chromasil" (trade mark) C_{18} column, eluant: acetonitrile, water and 0.1% trifluoroacetic acid) afforded 10 mg of the racemic title compound in 2.8 % yield.

^{1}HNMR (300 MHz, DMSO-d_6): δ 10.19 (1H, s); 8.08 (1H, s); 7.64 (2H, d, J = 8.55Hz); 7.07 (2H, d, J = 8.43 Hz); 5.98 (1H, d, J = 4.49 Hz); 4.57 (1H, d, J = 4.32 Hz); 1.40 (3H, s).

LC-MS (APCI) m/z = 337 ($MH^+ - H_2O$)

Example 15

(5R)-{[4-(2,2-Dioxo-2,3-dihydro-1H-2lambda*6*-benzo[c]thiophen-5-yl)-phenyl]-(R)-hydroxy-methyl}5-propyl-imidazolidine-2,4-dione



A mixture of 2-(2,2-dioxo-2,3-dihydro-1H-2lambda *6'-benzo[c]thiophen-5-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaboralane (300 mg, 1.02 mmol), 5-[hydroxy-(4-iodophenyl)-methyl]-5-propyl-imidazolidine-2,4-dione (555 mg, 1.48 mmol), sodium hydrogencarbonate (336 mg, 400 mmol) and palladium diacetate (catalytic amount) in acetone (10 ml) and water (10 ml) was deoxygenated 3 times (vacuum/nitrogen by manifold) and then stirred at 50°C for 75 minutes with nitrogen as a protective atmosphere. The slurry was partitioned between 1 M HCl (aq, 50 ml), ethyl acetate (50 ml) and heptane (50 ml). The organic phase was filtered trough Celite® filter aid and evaporated. Purification by reverse-phase HPLC ("Chromasil" (trade mark) C_{18} column, 50.8mm I.D x 250 mm L) using acetonitrile-water (0.1% TFA added) as eluant gave 0.020 g of the racemic title compound as a white solid. Chiral chromatography ("Chiralpak" (trade mark) AD-H column, ethanol/isohexane: 75/25, 6 ml/min flow, collecting fraction 1) afforded 0.007 mg of the title compound in 1.7 % yield.

LC-MS (APCI) m/z = 415.0 (MH^+)

Preparation of starting materials:

(R,R/S,S) 5-[Hydroxy-(4-iodophenyl)-methyl]-5-propyl-imidazolidine-2,4-dione

5-Propyl-hydantoin (2.842 g, 20 mmol), 4-iodo-benzaldehyde (4.651 g, 20 mmol) and trimethylamine (60% aqueous solution, 3.300 ml) was stirred for 16 hours at 80°C in

ethanol (30 ml) and water (20 ml). Water (18 ml) was dropped into the hot solution to afford a precipitate which was then filtered off to afford 1.664 g (22.2 % yield) of title compound as a 3:1 diastereomeric mixture.

^{1}HNMR 300 MHz (DMSO-d_6): δ 0.88 (t, 3H),1.29 8m, 2H), 1.91 (dt, 2H), 4.57 (d, 1H), 5.94 (d, 1H), 7.07 (d, 2H), 7.64 (d, 2H), 7.97 (s, 1H), 10.19 (s, 1H).
LC-MS (APCI) m/z = 375.1 (MH^+)

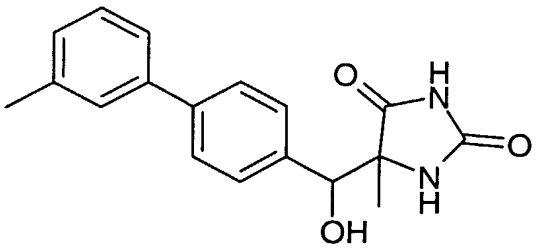
2-(2,2-Dioxo-2,3-dihydro-1H-2lambda *6'-benzo[c]thiophen-5-yl)-4,4,5,5-tetramethyl-[1,3,2]dioxaboralane

Prepared from commercially available 5-bromo-1,3-dihydro-benzo[c]thiophene 2,2-dioxide and methanesulfonic acid 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaboralan-2-yl)-naphthalen-2-yl ester (see Example 5 above).

^{1}HNMR 300 MHz (DMSO-d_6): δ 1.29 (s, 12H), 4.52 (d, 4H), 7.39 (d, 1H), 7.64 (d, 1H), 7.68 (s, 1H.
TLC (silica gel, ethyl acetate/heptane: 40/60, Rf = 0.17)

Example 16

(5R)-[(R)-Hydroxy-(3'-methyl-biphenyl-4-yl-)-methyl]-5-methyl-imidazolidine-2,4-dione



A mixture of toluene-3-boronic acid (47.2 mg, 0.33 mmol), (R,R/S,S)-5-[hydroxy-(4-iodophenyl)-methyl]-5-methyl-imidazolidine-2,4-dione (89.7 mg, 0.26 mmol), palladium diacetate (catalytic amount) and trimethylamine (60% aqueous solution, 0.100 ml) in

ethanol (3 ml) and water (1 ml) was deoxygenated (vacuum/nitrogen exchange by a manifold) and then stirred at 50°C for 60 minutes with nitrogen as protective atmosphere. The solution was partitioned between water and diethylether/ethyl acetate (1:1). Evaporation and reverse-phase HPLC ("Chromasil" (trade mark) C_{18} column, eluant: acetonitrile, water and 0.1% trifluoroacetic acid) afforded 5 mg of the racemic title compound in 1.6 % yield.

^{1}HNMR 300 MHz (DMSO-d_6): δ 1.42 (s, 3H), 2.35 (s, 3H), 4.65 (d, 1H), 5.90 (d, 1H), 7.15 (d, 1H), 7.31 (t, 1H), 7.33 (d, 2H), 7.41-7.46 (m, 2H), 7.55 (d, 2H), 8.09 (s, 1H), 10.16 (s, 1H).
LC-MS (APCI) m/z = 311 (MH+)

Preparation of starting materials:

(R,R/S,S)-5-[Hydroxy-(4-iodophenyl)-methyl]-5-methyl-imidazolidine-2,4-dione
4-Iodo-benzaldehyde (9.280 g, 40.0 mmol), 5-methyl-hydantoin (4.564 g, 40.0 mmol) and 45% aqueous solution of trimethylamine (6.40 ml, 40.0 mmol) was refluxed in ethanol (60 ml) and water (40 ml) for 20 hours under an atmosphere of nitrogen. A white precipitate was formed. After cooling at room temperature for approximately 15 minutes the precipitate was collected by filtration and then washed sequentially with ethanol (50%, 50 ml), water (50 ml) and diethyl ether (50 ml). Drying by air suction afforded the title compound (7.968 g, 23.0 mol, 57.5 % yield) as a white solid in the form of the pure racemate.

LC-MS (APCI) m/z = 346.9 [MH^+].

Pharmacological Example

Isolated Enzyme Assays

Recombinant human MMP12 catalytic domain may be expressed and purified as described by Parkar A.A. *et al*, (2000), Protein Expression and Purification, 20:152. The purified enzyme can be used to monitor inhibitors of activity as follows: MMP12 (50 ng/ml final concentration) is incubated for 60 minutes at room temperature with the synthetic substrate Mac-Pro-Cha-Gly-Nva-His-Ala-Dpa-NH_2 in assay buffer (0.1M "Tris-HCl" (trade mark) buffer, pH 7.3 containing 0.1M NaCl, 20mM $CaCl_2$, 0.020 mM ZnCl and 0.05% (w/v) "Brij 35" (trade mark) detergent) in the presence (5 concentrations) or absence of inhibitors. Activity is determined by measuring the fluorescence at λex 320nm and λem 405nm. Percent inhibition is calculated as follows: % Inhibition is equal to the [$Fluorescence_{plus\ inhibitor}$ - $Fluorescence_{background}$] divided by the [$Fluorescence_{minus\ inhibitor}$ - $Fluorescence_{background}$].

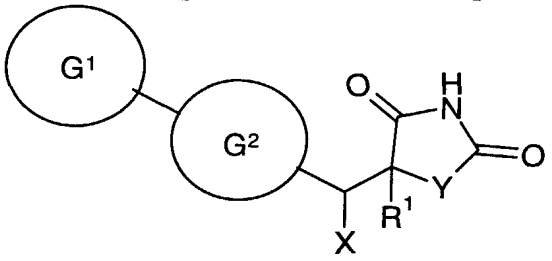
A protocol for testing against other matrix metalloproteinases, including MMP9, using expressed and purified pro MMP is described, for instance, by C. Graham Knight *et al.*, (1992) FEBS Lett. 296(3):263-266.

The following table shows the IC_{50} figures (in nanomolar) for a representative selection of the compounds of the examples when tested against MMP12 and MMP9.

Compound of Example No.	Human MMP12 IC_{50} (nm)	Human MMP9 IC_{50} (nm)
5	1.0	16.0
7	1.0	7.0
10	1.0	13.0
12	1.0	13.0
16	7.0	70.0

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof



(I)

wherein

X represents –OH, $-NH_2$, $-NH(C_1-C_3$ alkyl) or –SH;

Y represents $-NR^2$ where R^2 represents hydrogen or C_1-C_4 alkyl;

R^1 represents hydrogen, or a group selected from C_1-C_6 alkyl and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, each group being optionally substituted with at least one substituent selected from halogen, hydroxyl, cyano, carboxyl, $-NR^3R^4$, $-CONR^5R^6$, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylcarbonyl(oxy), $-S(O)_mC_1-C_6$ alkyl where m is 0, 1 or 2, C_1-C_6 alkylsulphonylamino, C_1-C_6 alkoxycarbonyl(amino), benzyloxy and a saturated or unsaturated 5- to 6-membered ring which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur, the ring in turn being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 alkoxycarbonyl and C_1-C_6 hydroxyalkyl;

R^3, R^4, R^5 and R^6 each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

G^2 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring;

G^1 represents a 5- or 6- membered aryl or heteroaryl monocyclic ring which may be optionally fused to a second ring to form a bicyclic ring system containing a total of 8- to 10-ring atoms, the monocyclic ring or fused bicyclic ring system being optionally substituted with at least one substituent selected from halogen, hydroxyl, oxo, cyano,

nitro, C_1-C_6 alkyl (optionally substituted by one or more of cyano, halogen, hydroxyl and methoxy), C_2-C_6 alkenyl, C_1-C_6 alkoxy (optionally substituted by one or more halogen atoms), -$S(O)_n$$C_1$-$C_6$ alkyl where n is 0, 1 or 2 (optionally substituted by one or more halogen atoms), C_1-C_6 alkylcarbonyl(amino) (optionally substituted by one or more halogen atoms), C_1-C_6 alkylcarbonyloxy, phenyl, benzyloxy, $-NR^7R^8$ and a group –V-U-W;

R^7 and R^8 each independently represent hydrogen or C_1-C_6 alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

V represents -CH_2, -OCH_2, -CH_2O, -O, -S, -SO, -SO_2, -O-SO_2, -SO_2-O, -NH, -NHC(O), -C(O)NH, -O-C(O)NH, -NHC(O)NH, -$NHSO_2$, -SO_2NH or -C(O);

U represents C_1-C_5 alkylene; and

W represents a direct bond to G^1 or a group selected from hydrogen, hydroxyl, amino, cyano, (di)C_1-C_3 alkylamino, C_1-C_3 alkylamido, C_1-C_3 alkylcarbamate, C_1-C_3 alkylurea, C_1-C_3 alkylsulphonyl, imidazolyl, oxazolyl and thiazolyl.

2. A compound according to claim 1, wherein X represents –OH.

3. A compound according to claim 1 or claim 2, wherein Y represents –NH.

4. A compound according to any one of claims 1 to 3, wherein R^1 represents hydrogen or C_1-C_4 alkyl optionally substituted with a carboxyl substituent group.

5. A compound according to any one of claims 1 to 4, wherein G^2 represents phenyl.

6. A compound according to any one of claims 1 to 5, wherein G^1 represents a 5- or 6-membered aryl or heteroaryl monocyclic ring optionally substituted in a *meta* and/or *para* position.

7. A compound according to claim 6, wherein the *meta* substituent is selected from C_1-C_3 alkyl and $-CH_2CN$.

8. A compound according to claim 6, wherein the *para* substituent is selected from Br, Cl, -CN, $-CF_3$, $-SCF_3$ and $-OCF_3$.

9. A compound according to any one of claims 1 to 5, wherein, in G^1, the bicyclic ring system is selected from quinolinyl, isoquinolinyl, indolyl, tetrahydroisoquinolinyl, benzofuranyl, benzothienyl, quinazolinyl, phthalazinyl, dihydrobenzofuranyl, naphthyl and dihydroindolyl.

10. A compound according to claim 1 which is selected from the group consisting of:

(R,R)/(S,S)-5-[(4-(1-Benzothien-2-yl)phenyl)(hydroxy)methyl]-5-methylimidazolidine-2,4-dione,

(*R*,*R*)/(*S*,*S*)-5-[[4-(1-Benzofuran-3-yl)phenyl](hydroxy)methyl]-5-methylimidazolidine-2,4-dione,

(R,R)/(S,S)-5-[Hydroxy(4´-methyl-1,1´-biphenyl-4-yl)methyl]-5-methylimidazolidine-2,4-dione,

(5*R*)-5-[(*R*)-Hydroxy(4-quinoline-6-ylphenyl)methyl]-5-methylimidazolidine-2,4-dione trifluoroacetate,

(R,R)-Methanesulfonic acid 6-{4-[hydroxy-(4-methyl-2,5-dioxo-imidazolidin-4-yl)-methyl]-phenyl}-naphthalen-2-yl ester,

(5*R*)-5-[(*R*)-Hydroxy(4-isoquinoline-6-ylphenyl)methyl]-5-methylimidazolidine-2,4-dione trifluoroacetate,

(5*R*)-5-{(*R*)-Hydroxy[4-(6-hydroxy-2-naphthyl)phenyl]methyl}-5-methylimidazolidine-2,4-dione,

(5*R*)-5-[(*R*)-(4-{6-[2-(Dimethylamino)ethoxy]-2-naphthyl}phenyl)(hydroxy)methyl]-5-methylimidazolidine-2,4-dione hydrochloride,

(5*R*)-5-[(*R*)-Hydroxy(4-{6-[2-(methylsulfonyl)ethoxy]-2-naphthyl}phenyl)methyl]-5-methylimidazolidine-2,4-dione,

4'-[(2,5-Dioxoimidazolidin-4-yl)(hydroxy)methyl]-3-methyl-1,1'-biphenyl-4-carbonitrile,

4'-[Hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)methyl]-3-methyl-1,1'-biphenyl-4-carbonitrile,

{4'-[Hydroxy-(4-methyl-2,5-dioxoimidazolidin-4-yl)-1,1'-biphenyl-3-yl}acetonitrile,

5-(Hydroxy{4-[2-(trifluoroacetyl)-1,2,3,4-tetrahydroisoquinoli-6-yl]phenyl}methyl)-5-methylimidazolidine-2,4-dione,

(R,R/S,S)-3-[4-(Biphenyl-4-yl-hydroxy-methyl)-2,5-dioxo-imidazolidin-4-yl]-propionic acid,

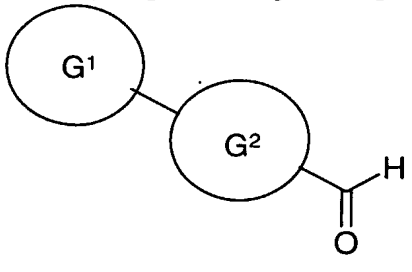
(5R)-{[4-(2,2-Dioxo-2,3-dihydro-1H-2lambda*6*-benzo[c]thiophen-5-yl)-phenyl]-(R)-hydroxy-methyl}5-propyl-imidazolidine-2,4-dione,

(5R)-[(R)-Hydroxy-(3'-methyl-biphenyl-4-yl-)-methyl]-5-methyl-imidazolidine-2,4-dione,

and pharmaceutically acceptable salts and solvates thereof.

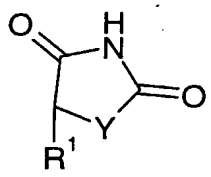
11. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in claim 1 which comprises,

(a) when X represents a hydroxyl group, reacting a compound of formula



(II)

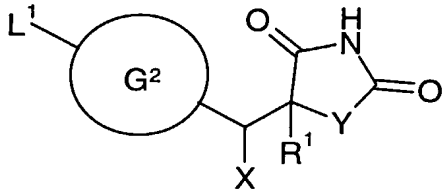
wherein G^1 and G^2 are as defined in formula (I), with a compound of formula



(III)

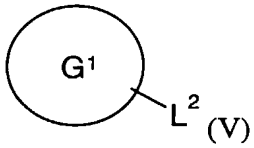
wherein Y and R^1 are as defined in formula (I); or

(b) reacting a compound of formula



(IV)

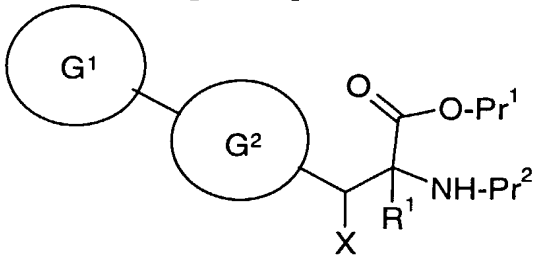
wherein L^1 represents a suitable leaving group and X, Y, R^1 and G^2 are as defined in formula (I), with a compound of formula



(V)

wherein L^2 represents a suitable leaving group and G^1 is as defined in formula (I) under Suzuki or Stille coupling reaction conditions; or

(c) when Y represents NH, reacting a compound of formula



(VI)

wherein Pr^1 represents hydrogen or a suitable carboxyl protecting group, Pr^2 represents hydrogen or a suitable amine protecting group and X, R^1, G^1 and G^2 are as defined in formula (I), with an alkali metal or alkaline earth metal cyanate under acidic conditions; and optionally after (a), (b) or (c) forming a pharmaceutically acceptable salt or solvate.

12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A process for the preparation of a pharmaceutical composition as claimed in claim 12 which comprises mixing a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as defined in any one of claims 1 to 10 with a pharmaceutically acceptable adjuvant, diluent or carrier.

14. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 for use in therapy.

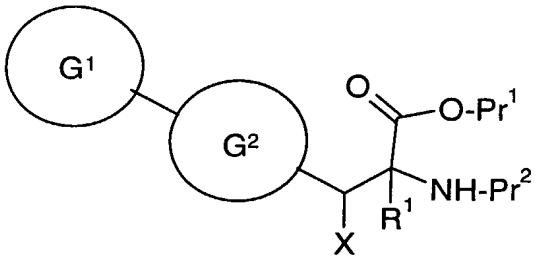
15. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10 in the manufacture of a medicament for use in the treatment of an obstructive airways disease.

16. Use according to claim 15, wherein the obstructive airways disease is asthma or chronic obstructive pulmonary disease.

17. A method of treating a disease or condition mediated by MMP12 and/or MMP9 which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10.

18. A method of treating an obstructive airways disease which comprises administering to a patient a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof as claimed in any one of claims 1 to 10.

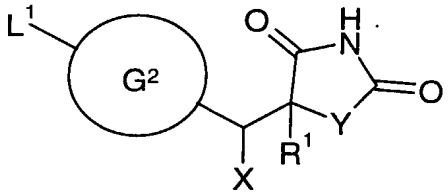
19. An intermediate compound of formula



(VI)

wherein Pr^1 represents hydrogen or a suitable carboxyl protecting group, Pr^2 represents hydrogen or a suitable amine protecting group and X, R^1, G^1 and G^2 are as defined in formula (I) according to claim 1.

20. An intermediate compound of formula



(IV)

wherein L^1 represents a suitable leaving group and X, Y, R^1 and G^2 are as defined in formula (I) according to claim 1.

21. An intermediate according to claim 20, wherein L^1 represents iodine, X represents OH which is optionally protected by a protecting group, Y represents NH and G^2 represents phenyl.

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(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GABOS, Balint** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **LUNDKVIST, Michael** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **MUNCK AF ROSENSCHÖLD, Magnus** [SE/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE). **SHAMOVSKY, Igor** [CA/SE]; AstraZeneca R & D Lund, S-221 87 Lund (SE).

(74) Agent: **ASTRAZENECA AB**; Global Intellectual Property, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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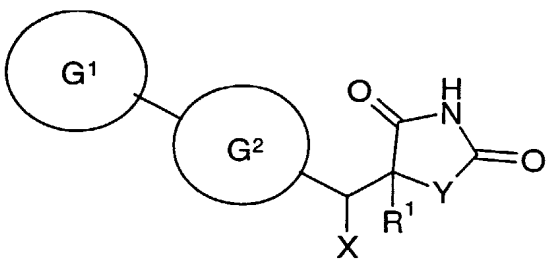
Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

(88) Date of publication of the international search report:
24 June 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METALLOPROTEINASE INHIBITORS AND INTERMEDIATES FOR PREPARATION THEREOF



(I)

(57) Abstract: The invention provides compounds of formula, in which X, Y, R^1, G^1 and G^2 have the meanings defined in the specification; processes for their preparation; pharmaceutical compositions containing them; a process for preparing the pharmaceutical compositions; and their use in therapy.

WO 2004/024060 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001406

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 409/10, C07D 233/78, C07D 401/10, A61K 31/4178, A61K 31/4166, A61P 19/00, A61P 17/00, A61P 37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, EPO-INTERNAL, CHEM.ABS.DATA, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02074750 A1 (ASTRAZENECA AB), 26 Sept 2002 (26.09.2002)	1-18,20-21
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P,X	WO 02074752 A1 (ASTRAZENECA AB), 26 Sept 2002 (26.09.2002)	1-18
	--	
X	EP 1191024 A1 (TSCHESCHE, HARALD ET AL), 27 March 2002 (27.03.2002), examples 23-26, page 5	1-18
	--	
X	Heterocytes, Volume 52, No. 3, 2000, Piero Dalla Croce et al, "Stereoselective aldol addition of a chiral glycine enolate synthon to heteroaromatic aldehydes", pages 1337-1344, page 1340, 5e	19
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 February 2004	10 -02- 2004
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund/BS Telephone No. +46 8 782 25 00

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File ACS, Accession no. 1994:299315, Document no. 120:299315, Sakamoto, Shuichi et al, "Preparation of pyridylserine derivatives as psychotropics", WO,A1,9320053,19931014, see CAS RN 154696-31-8, 154697-48-0	19
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X	Analytical sciences, Volume 7, Supplement 1991, Riichiro Nakajima et al, "The utility of 4-(2-thienyl)pyridines as a derivatization reagent for hplc and ce", pages 177-180, see page 178, No. 11	19
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X	Tetrahedron, Volume 48, No. 7, 1992, Takashi Owa et al, "Man-Designed Bleomycins: Significance of the Binding Sites as Enzyme Models and of the Stereochemistry of the Linker Moiety", pages 1193-1208, page 1205, No. 10	19
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X	Bull. Chem. Soc. Jpn. Volume 59, 1986, Toshiaki Miyake et al, "Studies on Glycosylation of erythro-Beta-Hydroxy-L-histidine. A Key Step of Bleomycin Total Synthesis", pages 1387-1395, page 1388, No. 14	19
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X	Tetrahedron Letters, Volume 23, No. 5, 1982, Sei-ichi Saito et al, "A new synthesis of deglyco-bleomycin A2 aiming at the total synthesis of bleomycin", pages 529-532, page 529, No. 7	19
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X	GB 1117616 A (WARNER-LAMBERT PHARMACEUTICAL COMPANY), 19 June 1968 (19.06.1968), page 8, preparation H	19
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INTERNATIONAL SEARCH REPORT

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2745875 A (GUSTAV EHRHART ET AL), 15 May 1956 (15.05.1956), column 5, example 8, lines 58-59, 61, 64-66	19
	--	
A	Chem. Rev., Volume 99, 1999, Mark Whittaker et al: "Design and Therapeutic Application of Matrix Metalloproteinase Inhibitors", page 2735 - page 2776	1-18
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2003/001406

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-18
because they relate to subject matter not required to be searched by this Authority, namely:

see extra sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see extra sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Box II.1

Claims 17-18 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

Box III

In order to fulfil the requirements of unity of invention as required by Rules 13.1, 13.2 and 13.3 PCT, it is necessary that the intermediate compounds are closely interconnected with the end products. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate compound. However, the present application lacks a single general inventive concept based on the above principle. This leads to the presence of the subjects listed above, each falling under its own restricted inventive concept.

The International Search Authority considers therefore that there are 2 inventions covered by the claims indicated as follows:

I: Claims: 1-18, 20-21 directed to compounds of formula I, processes for preparation, uses thereof and intermediates of formula IV.

II: Claim 19, directed to intermediate compounds of formula VI

WO	02074750	A1	26/09/2002	AU	5282101	A	26/11/2001
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				NO	20034044	D	00/00/0000
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				FR	1457622	A	24/01/1966
				GB	1117617	A	19/06/1968
				SE	322207	B	06/04/1970
US	2745875	A	15/05/1956	NONE			